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**A COLLECTION OF STUDIES ON THE BIOMETRY OF MYOPIC AND NON-MYOPIC
EYES**

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Doctor of Philosophy

ASTON UNIVERSITY

September 2016

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SUMMARY

At present, a wealth of interest surrounds the epidemiology of ametropia and ocular structural and functional correlates across the spectrum of refractive error. Myopia is the most common ocular condition globally, and its prevalence is continuing to increase. Myopia is not a purely refractive condition, being a major cause of visual impairment and blindness worldwide. Consequently, numerous studies have investigated various optical and non-optical interventions to limit its progression in childhood. This thesis describes the correlates of structural and functional parameters on the development of myopia in children. The investigation of these differences is expected to aid a deeper understanding of the aetiology of ametropia and subsequently assist with myopia amelioration.

The data presented within form a collection of cross-sectional cohort studies, investigating ocular parameters of children and young adults with normally developing eyes and children with peripheral retinal anomalies. Measures of central and peripheral refractive error, visual fields, fundus imaging and ocular biometry are analysed and discussed.

This thesis demonstrates that gender and ethnicity do not appear to have a significant influence on refractive error: axial length ratio. Furthermore, the distribution and degree of corneal or refractive astigmatism in children appears linked to increasing spherical hypermetropia and is not influenced by ethnicity, gender or axial length. Pilot work also suggests that Retinitis Pigmentosa and Congenital Stationary Night Blindness are appropriate models for the investigation of the retinal periphery's role in myopia development. The final study contained within found a reduction in foveal light sensitivity correlated with increasing myopia, perhaps suggestive of an increase in photoreceptor spacing.

It is, therefore, recommended that normative refractive, astigmatism and axial length data should be tailored to individual characteristics. Future large-scale longitudinal studies should be designed to develop growth curves for axial length and refractive error such as those available for anthropometric characteristics.

Keywords: Refractive error, axial length, peripheral refraction, perimetry, retinal pathology

ACKNOWLEDGEMENTS

I wish to thank my supervisors, Dr Nicola Logan and Dr Robert Cubbidge for their continued support and guidance over the course of my studies. Additionally, I would like to thank Mr John Ainsworth, Mr Manoj Parulekar and the staff at Birmingham Children's Hospital for their help and persistence with recruitment. I would like to extend a particular thank you to Mrs Laura Ramm, who went over and above for me throughout. Further thanks go to Dr Parth Shah and Dr Logan's research team, who collected data analysed in this thesis.

I would like to thank all of the students, the children, and their families for their involvement, patience and interest in the studies that make up this thesis.

I am also very grateful to the College of Optometrists for awarding me with a three-year Postgraduate Research Scholarship to fund this research.

I would like to give special thanks to my family and my friends for supporting me throughout this process. To Susie Jones, with whom I shared this experience and to Becca Savva, who were always there with unswerving support and good advice. Finally, I am incredibly grateful to my parents, Robert and Allison and my sisters Rosemary and Helen for their encouragement, love and help. Thank you.

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LIST OF ABBREVIATIONS

AC/A	Ratio of the accommodative convergence (AC) to the stimulus to accommodation (A)
ACD	Anterior chamber depth
AES	Aston Eye Study
ATR	Against the rule
AXL	Axial length
CA/C	Ratio of the convergence accommodation (CA) to the stimulus to convergence (C)
CHAID	Chi - squared automatic interaction detection
CI	Confidence interval
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
COMET	Correction of Myopia Evaluation Trial
cm	Centimetres
CR	Corneal curvature
CSNB	Congenital Stationary Night-Blindness
D	Dioptres
dB	Decibels
DC	Dioptres cylinder
DISC	Defocus Incorporated Soft Contact
DS	Dioptres sphere
DTA	Decision tree analysis
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study

F	Female
FEVR	Familial Exudative Vitreo-Retinopathy
HES	Hospital eye service
HFA	Humphrey Field Analyser
ILM	Internal limiting membrane
I	Inferior
IN	Inferior nasal
IOP	Intra-ocular pressure
IQR	Interquartile range
IT	Inferior temporal
J₀	Cartesian vector form of astigmatism with axis set to 90 degrees
J₄₅	Cartesian vector form of astigmatism with axis set to 180 degrees
kg	Kilograms
Kurt.	Kurtosis
LCD	Liquid crystal display
L	Left
LE	Left eye
logMAR	Logarithm of the minimum angle of resolution
M	Male
m	Metres
Max	Maximum
Min	Minimum
mm	Millimetres
mmHg	Millimetres of Mercury
MRI	Magnetic resonance imaging
MSE	Mean spherical equivalent

MWU	Mann – Whitney U
N	Nasal
n	Sample size
NHANES	National Health and Nutritional Examination Survey
NHS	National Health Service
NICER	Northern Ireland Childhood Errors of Refraction
NRES	National Research Ethics Service
OBL	Oblique
OLSM	Orinda Longitudinal Study of Myopia
<i>p</i>	Probability
PAL	Progressive addition lens
PCI	Partial coherence interferometry
pH	Logarithmic measure of Hydrogen ion concentration
PR	Peripheral refraction
RAF	Royal Air Force
R	Right
RE	Right eye
ROP	Retinopathy of Prematurity
RP	Retinitis Pigmentosa
RPE	Retinal pigment epithelium
<i>r_s</i>	Spearman rank - order coefficient
S	Superior
SD	Standard deviation
SMS	Sydney Myopia Study
SN	Superior nasal
SNR	Signal to noise ratio

Skew.	Skewness
SSI	Severely sight impaired
STAMP	Study of Theories about Myopia Progression
ST	Superior temporal
T	Temporal
UK	United Kingdom
USA	United States of America
VA	Visual acuity
WHO	World Health Organisation
WTR	With the rule
χ^2	Chi square
Z	Z score for skewness or kurtosis
°	Degrees
&	And
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
%	Percentage
±	Plus or minus
Δ	Prism dioptres
²	Square
λ	Wavelength

1. LITERATURE REVIEW

1.1 Myopia background

1.1.1 Definition of myopia

Refractive errors occur as a result of the inaccurate focusing of light rays, induced by a structural anomaly of the eye's optical system. Myopia refers to the portion of the refractive error spectrum in which parallel light entering the eye is brought to a focus before reaching the retinal plane, resulting in the perception of a blurred visual image (Atchison and Smith, 2000; Rabbetts, 2007).

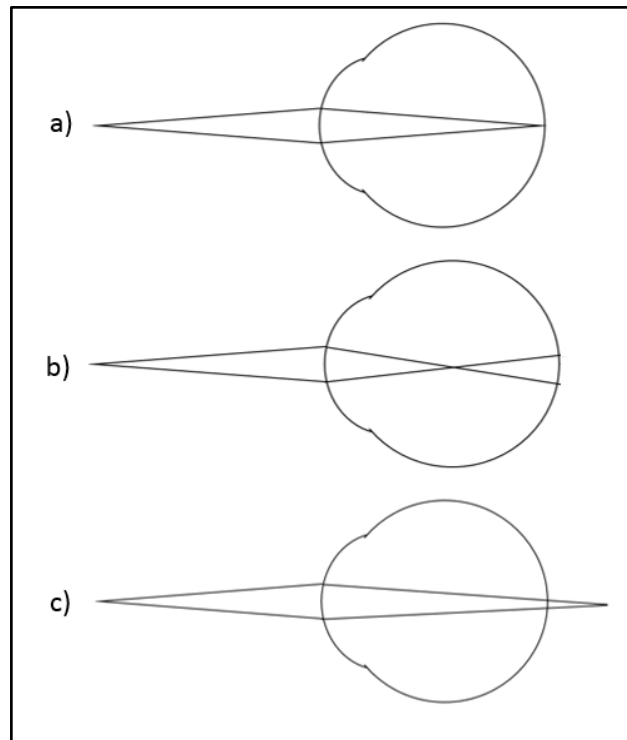


Figure 1.1 Schematic drawing of the focal points of the a) emmetropic, b) myopic and c) hyperopic eye.

The degree of myopia is determined by the distance by which the focal point is removed anteriorly from the retina. Visual acuity in myopia can be restored with the use of

corrective lenses, by compensating for the focusing error via the introduction of a divergent element into the optical system.

There is a broad range of ocular anomalies that can precipitate myopia including the corneal and crystalline lens surface curvature, refractive index gradient of the crystalline lens, and anterior and posterior chamber depth. Of these, increased posterior chamber depth (termed axial myopia) is the sole causative factor in the majority of cases (Tian *et al.*, 2011), as myopic eyes are generally larger and longer than emmetropic eyes (Atchison *et al.*, 2004; Logan *et al.*, 2004b). Axial myopia occurs owing to a discrepancy between the length of the eye and its dioptric focusing ability.

Along with axial myopia, other subdivisions by myopia aetiology are index and refractive myopia, each having a different underlying mechanism by which myopic blur is created. Refractive myopia is classified as myopia that is propagated by alterations in the refractive power of one or several of the refractive elements of the eye. Index myopia is a result of variations in the refractive index of the ocular media.

1.1.2 Prevalence of myopia

The prevalence of myopia has increased in recent decades worldwide (Bar Danyan *et al.*, 2005; Durkin *et al.*, 2007; Holden *et al.*, 2016; Morgan and Rose, 2005; Vitale *et al.*, 2009) reaching epidemic levels in some countries. Myopia now represents the most common ocular condition (Whatham *et al.*, 2009) and high myopia the leading cause of vision loss globally (Saw, 2006). In 2008 it was estimated by the WHO that 153 million people over five years were visually impaired due to uncorrected myopia and other refractive errors, and out of these, eight million people were blind (Resnikoff *et al.*, 2008). A more recent paper published by the NICER study group estimated that myopia prevalence in UK children aged ten to 16 years has more than doubled over the past 50

years (McCullough *et al.*, 2016). It is estimated that by the year 2050, world myopia prevalence will have increased from two billion in 2010 to five billion (half of the world population) (Holden *et al.*, 2015). Of these five billion people, almost one billion will be highly myopic, with a refraction of more than - 5.00 D (Holden *et al.*, 2015).

The population prevalence of myopia is not uniform across nations. Until recently, myopia was only deemed to be epidemic in parts of Asia (Lam *et al.*, 2004; Lin *et al.*, 2004; Saw, 2006). In urbanised areas of Japan, the prevalence of myopia has been reported as high as 40% (Sawada *et al.*, 2008), in Taiwan 50% (Lin *et al.*, 2004) and 70% in Singapore (Wu *et al.*, 2001). Differences in prevalence are also found within countries, with urban areas being more affected than rural communities (Flitcroft, 2014; Pan *et al.*, 2013; Park and Congdon, 2004; Thorn *et al.*, 2005a). In Asia, the prevalence commonly reaches over 80% in industrial centres (Pan *et al.*, 2012) and highly educated groups (Lin *et al.*, 2004; Woo *et al.*, 2004; Wu *et al.*, 1999).

However, mounting evidence exists to suggest that Western and Northern Europe (Parsinen *et al.*, 2012; Williams *et al.*, 2015) as well as other non - Asian countries including but not exclusive to the USA (Lee *et al.*, 2002; Vitale *et al.*, 2008; Wang *et al.*, 1994), Australia (Rose *et al.*, 2001) and Israel (Bar Danyan *et al.*, 2005) are now experiencing a rapid rise in the prevalence of both high myopia and myopia in general. In 2007, it was estimated that over a third of the UK adult population were myopic (Simpson *et al.*, 2007). Further evidence for an increase in myopia prevalence in Europe comes from the work of the E³ Consortium where refractive data for 61,946 adult participants (age range 44 to 78 years) was compiled from 15 population-based studies performed between 1990 and 2013 (Williams *et al.*, 2015). The study found a significant cohort effect for increasing myopia prevalence across more recent birth decades. Age standardised myopia prevalence was found to increase from 17.8% in those born

between 1910 and 1939, to 23.5% in those born between 1940 and 1979 (Williams *et al.*, 2015).

Studies of refractive error in childhood have found that myopia is an increasingly common finding throughout the school years into early adulthood (Goh *et al.*, 1994; Goldschmidt *et al.*, 2003; Jorge *et al.*, 2007; Kinge *et al.*, 1999; Tan *et al.*, 2000; Saw *et al.*, 2002). Though myopia in the early years of life is rare, there has been an increase in the number of children who have early / juvenile onset myopia (Morgan and Rose, 2005), that is, myopia which occurs and progresses between the age of six and the teenage years (Grosvenor, 1987a).

Autorefraction data from the USA National Health and Nutrition Examination Survey (NHANES), showed a higher prevalence of myopia in women (53.9%) than men (46.6%) aged 20 - 39 years, but no significant difference was found for any other age group (Vitale *et al.*, 2008).

1.1.3 Classification of myopia

1.1.3.1 Classification by degree of myopia

There is debate over the minimum level of refractive error that constitutes myopia, though this is generally for academic and research purposes. The classification of myopia by the degree of manifest refractive error is possibly the most clinically relevant way, as a structural measurement is not always available, and a detailed refractive history is not always obtainable. It is important to note that there is a risk of overestimating low levels of myopia due to a lack of cycloplegia, for example, instrument myopia.

Although the exact grading boundaries vary from practitioner to practitioner, myopia is often defined as a refractive error of - 0.50 D or more. Up to - 3.00 D is considered low

myopia, - 3.00 D to - 6.00 D is moderate and greater than 6.00 D and 10.00 D are high and very high myopia respectively (Baird, 2010). It is important to appreciate that discrepancy may occur here depending on which meridian is used to determine which grouping is appropriate. For research purposes, it is most common for the mean spherical error to be used for classification or the most myopic meridian.

1.1.3.2 Classification by age of onset

It is a long-standing clinical observation that in the majority of cases, the earlier the manifestation of myopia the greater the progression and the higher the degree of eventual refractive error one will exhibit in adulthood (Blegvad, 1927, Mäntyjärvi, 1985). Grosvenor (1987a) was the first to advocate this as a method of classification where he categorised myopia onset into four groups; congenital, early/juvenile onset, early - adult onset and late - adult onset.

Congenital myopia describes myopia that is present in infancy and is maintained into school age. Juvenile onset myopia encompasses individuals who present with myopia between age six and their teenage years. Early adult onset is myopia that presents between 20 to 40 years and onset after the age of 40 is classified as late adult onset (Grosvenor, 1987a).

1.1.3.3 Classification by associated pathology

An important distinction to make is whether a person's myopia is a result of normal physiological variation or whether there is an association with disease processes – the latter termed pathological myopia (Verkicharla *et al.*, 2015). Physiological myopia refers to that which occurs as a normal variant of the ocular development process, where there is an anomaly in the coordination of the ocular refractive structures, yet the individual elements are inherently normal. Pathological myopia in comparison is a continuation of

physiological myopia that fails to halt when normal ocular growth would, and is the most severe form of myopia (Wong *et al.*, 2014). It is important to note a further classification here – acquired myopia, where the refractive error is a result of pathology not associated with ocular development – such as cataracts and diabetes mellitus.

General population studies in Chinese cohorts have found a prevalence of myopic retinopathy of 3.1% (Liu *et al.*, 2010) and 0.9% (Gao *et al.*, 2011). A study of a Japanese cohort found a prevalence of 1.7% (Asakuma *et al.*, 2012), a Taiwanese cohort 1.7% (Chen *et al.*, 2012) and an Australian cohort 1.2% (Vongphanit *et al.*, 2002). These studies are described in more detail in Table 1.1.



Table 1.1 Prevalence of pathological myopia. Reproduced with permission (Verkicharla *et al.*, 2015) [Current and predicted demographics of high myopia and an update of its associated pathological changes, Verkicharla, P. K., Ohno-Matsui, K. and Saw, S. M. Ophthalmic and Physiological Optics Vol. 35, Copyright © 2015 The College of Optometrists].

Also of concern are the potential degenerative consequences of myopia. An association has been found between myopia and degenerative changes including retinal detachment, glaucoma, myopic maculopathy and chorioretinal changes (Flitcroft, 2012; Saw *et al.*, 2005). Although any level of myopia can potentially precipitate degenerative change, eyes with myopic refractive errors over 6.00 D are the most susceptible (Saw, 2006). The Australian Blue Mountains Eye Study (Vongphanit *et al.*, 2002) found that population prevalence of pathological myopia increased from approximately 1% in low

myopes (≤ -3.00 D) to over 50% in high myopes (≤ -9.00 D). An even greater disparity has been found in Chinese populations, with the Beijing (Liu *et al.*, 2010) and Handan (Gao *et al.*, 2011) Eye Studies both finding a prevalence in low myopes of 1 - 19% rising to 70% in high myopes.

The latest definition for the diagnosis and classification of pathological myopia is provided by the METAanalysis for Pathologic Myopia study (Ohno-Matsui *et al.*, 2015), which has five distinct categories based on signs of myopic maculopathy. These stages are described in Table 1.2. According to this classification system, pathological myopia is only present when signs are of grade two and above.



Table 1.2 Grading of pathological myopia according to the 'METAanalysis for Pathologic Myopia Study' Redrawn from (Ohno-Matsui *et al.*, 2015). [International photographic classification and grading system for myopic maculopathy, Ohno-Matsui, K., Kawasaki, R., Jonas, J. B., Cheung, C. M., Saw, S. M., Verhoeven, V. J., Klaver, C. C., Moriyama, M., Shinohara, K., Kawasaki, Y., Yamazaki, M., Meuer, S., Ishibashi, T., Yasuda, M., Yamashita, H., Sugano, A., Wang, J. J., Mitchell, P., Wong, T. Y. and META-analysis for Pathologic Myopia (META-PM) Study Group. *Am J Ophthalmol.* *Am J Ophthalmol.* *Am J Ophthalmol.* Vol. 159, Copyright © 2015 Elsevier Inc.].

Pathological myopia demonstrates a distinctly more unstable progression than physiological cases and is one of the most frequent causes of secondary blindness in the world (Takahashi *et al.*, 2012). Flitcroft (2012), suggested that there is, in fact, no safe level of myopia, with the risk of developing ocular pathologies at low levels of myopia being found to be comparable to systemic disorders. Myopias between -1.00 D and

- 3.00 D hold an increased risk of cataract and glaucoma. The risks of developing cataract or glaucoma associated with myopia were found to be similar to the risk of stroke in individuals who smoke over 20 cigarettes daily. It was also found that myopia carries a far greater risk for myopic maculopathy and retinal detachment than any known population risk factor for cardiovascular disease (Flitcroft, 2012).

1.2 Human emmetropisation

1.2.1 Background

Emmetropia is a rare finding in the neonate (Cook and Glasscock, 1951), with most demonstrating significant refractive errors, notably hyperopia, which is considered to be normal rather than being an exception during early development (Wildsoet, 1997). However, these ametropias generally disappear throughout childhood as a consequence of ocular development and growth (Mutti *et al.*, 2005). The mechanism by which there is structural compensation of ocular components eventuating in an emmetropic refractive error despite axial elongation is termed emmetropisation (McBrien and Barnes, 1984).

Emmetropisation can be considered as a departure from a Gaussian (normal) distribution of refractive error at birth (McBrien and Barnes, 1984; Robinson, 1999), to a leptokurtic distribution that has a significant skew towards emmetropia (Sorsby *et al.*, 1957; Sorsby *et al.*, 1961; Trollo, 1992) (see Figure 1.2). The pattern of refractive error distribution in adults whereby there is a greater than expected frequency of emmetropia strongly suggests the existence of a mechanism that governs ocular and refractive state development (Flitcroft, 2014).



Figure 1.2 Refractive error frequency distributions. Data for newborns (Cook and Glasscock, 1951) and children between six and eight years are plotted (Kempf *et al.* 1928). Reproduced with permission (Smith, 1998) [Spectacle lenses and emmetropization: the role of optical defocus in regular ocular development, Smith, E. L. 3rd. Optometry and Vision Science Vol. 75, Copyright © 1998 American Academy of Optometry].

Though emmetropisation is considered to be a generally successful process (Sorsby and Leary, 1970), in some cases there can be a derailment of emmetropisation, or a failure to maintain emmetropia once achieved, resulting in significant myopic refractive errors into adulthood. Refractive variations can be partially attributed to genetics and physiological discrepancies in the coordination amongst normally distributed ocular structures, as a consequence of globe enlargement. However, animal studies have provided convincing evidence that eye growth is not an entirely passive process, and indicate the existence of an actively regulated vision dependent mechanism (Norton, 1999; Smith *et al.*, 1998; Wallman and Winawer, 2004; Wildsoet, 1997), which exerts feedback control to regulate the growth of one or more of the ocular parameters.

1.2.2 Phases of emmetropisation

Sorsby and Leary (1970) identified that the pace of eye growth was irregular over the period leading to ocular maturity and divided emmetropisation into two discrete phases: the rapid infantile and the slow juvenile phase.

1.2.2.1 Rapid infantile phase

The rapid infantile phase is the description made by Sorsby and Leary (1970) to describe the period between birth and three years where the structures of the eye must compensate to reduce ocular refracting power by approximately 20 dioptres to account for an axial length (AXL) increase of 5 mm. Both cross-sectional and longitudinal studies have suggested that the majority of emmetropisation occurs between the first three and nine months of life (Mayer *et al.*, 2001; Mutti *et al.*, 2005; Pennie *et al.*, 2001). The reduction in ametropia appears to occur very rapidly over this period and is concomitant with a reduction in population variance (Mutti *et al.*, 2005). A transformation from a Gaussian distribution at three months to a leptokurtic distribution at nine months is clearly observable in Mutti *et al.*'s (2005) study. Figure 1.3 shows the distribution of refraction in studies by Mutti *et al.*, 2005, and Ingram and Barr, 1979, for age groups between three months and three and a half years.



Figure 1.3 Four distributions of refraction from two different studies (a) Mutti *et al.*, 2005 and (b) Ingram and Barr (1979) from 3 months of age to 3.5 years (a) 3 - 9 months. (b) 1 - 3 years. Reproduced with permission (Flitcroft, 2014) [Emmetropisation and the aetiology of refractive errors, Flitcroft, D. I. Eye Vol. 28, Copyright © 2014 Macmillan Publishers Limited].

From these graphs, it is again clear that there is a progressive myopic shift in refraction and a significant reduction in the variability of refraction in this period. It is also clear that although the population as a whole is generally falling within a Gaussian distribution, the children who fall outside of this distribution are predominantly hyperopic (see Figure 1.3, these bars are shaded in dark grey). These subjects with higher levels of hyperopia are either emmetropising at a significantly slower rate or have failed to emmetropise altogether, and have been effectively 'left behind' as the rest of the subject's refractions are moving towards emmetropia (Flitcroft, 2014).

Saunders *et al.* (1995) performed modified Mohindra retinoscopy on 22 subjects in the first six months of life and again between 12 and 17 months of age. Subjects at baseline were selected according to the level of refractive error to be representative of the range of initial spherical ametropias between + 1.25 D and + 4.25 D. No child was observed to be myopic at baseline. The findings are depicted in Figure 1.4.

These results are unambiguous in showing that it is normal for infants with normal visual development to initially exhibit high levels of hyperopia that then decrease steeply over the first year of life. This work makes it clear that emmetropisation is a process capable of achieving a significant reduction in the spread of ametropia between birth and 17 months.



Figure 1.4 Individual data illustrating the change in ametropia between an initial refraction at zero to five months of age and a subsequent refraction during 12 - 17 months of age. Solid lines join data from the same subject. Reproduced with permission (Saunders *et al.*, 1995) [Early refractive development in humans, Saunders, K. J., Survey of Ophthalmology, Vol. 40, Copyright © 1995 Survey of Ophthalmology].

The studies of both Saunders *et al.* (1995) and Mutti *et al.* (2005) indicate that higher initial degrees of hyperopia are associated with faster rates of refractive recovery. Though the work of Saunders *et al.* (1995) included no biometric data, AXL has been shown to change during the rapid infantile phase (Fledelius and Christensen, 1996) and the reduction in ametropia detailed in Mutti *et al.*'s 2005 paper was coincident with an increased rate of axial elongation.

Biometric data have shown that corneal (Inagaki, 1986; Mutti *et al.*, 2005) and lenticular power (Gordon and Donzis, 1985; Mutti *et al.*, 2005) reduce in the rapid infantile phase, however, there is still a reduction in net hyperopia. This is indicative of a relationship whereby corneal and lenticular modulation is dependent on axial elongation, and that axial growth is the leading force and the pivotal structure implicated in the decrease in ametropia in this early period (Mutti *et al.*, 2005).

Alongside the reduction in spherical refractive error in the first few years of life, there is also a significant reduction in astigmatism (Abrahamsson *et al.*, 1988; Gwiazda *et al.*, 1984; Gwiazda *et al.*, 2000, Hirsch *et al.*, 1963) which appears to be uncorrelated to the change in spherical ametropia (Ehrlich *et al.*, 1997).

Emmetropisation begins to slow after the first three years of life, but by six years, most populations have achieved a clear leptokurtic distribution (French *et al.*, 2012; Ojaimi *et al.*, 2005; Watanabe *et al.*, 1999). However, the distribution is positively skewed due to a higher proportion of hyperopes compared to the negative skew seen in adult populations (Flitcroft, 2014). Flitcroft (2014) stated that *'if emmetropisation is considered to be the process whereby human refractive errors are minimised, then this process would appear to be largely complete by this age in terms of spherical refractive error, astigmatism and anisometropia'* (Gwiazda *et al.*, 2000; Deng and Gwiazda, 2012).

1.2.2.2 Slow juvenile phase

The slow juvenile phase represents the period between approximately three and 13 years of age where corneal and lens compensation continues. However, this is at a much slower rate as there is only a 1 mm increase in AXL (Sorsby and Leary 1970). In most populations that have been studied, there is a change from the positively skewed leptokurtic distribution present at the end of the rapid infantile phase, with an increase in myopia leading to a negative skew, a reduction in leptokurtosis and an increase in variance (Flitcroft, 2014). However, a continuation of emmetropisation has been found in studies of populations in Australia (French *et al.*, 2012) and Vanuatu (Garner *et al.*, 1988), leading to a low incidence of myopia and hyperopia (Flitcroft, 2014).

The increase in variance, reduction in leptokurtosis and negative skew is most pronounced in Eastern populations where there is a high prevalence of myopia and the fastest rise

in prevalence (Flitcroft, 2014). There is evidence that in these populations, the shift towards myopia appears as early as six years old (Lin *et al.*, 2004; Matsumura and Hirai, 1999). However, a longitudinal study conducted in Japan over 13 years showed that an increase in myopia prevalence from 49.3% to 65.6% was not reflected by any disruption of early emmetropisation, with the change in distribution only becoming apparent after five years (Matsumura and Hirai, 1999).

The majority of physiological myopia results from a derailment of the emmetropisation process during the slow juvenile phase (Grosvenor, 1987b) with myopic errors becoming especially evident at the pivotal age of around nine years. Myopia which onsets after the age of six years has been found to occur as a rapid spurt of myopic shift following several years of relative stability in refraction or a slow decline in refractive error (Flitcroft, 2014; Mantyjarvi, 1985; Thorn *et al.*, 2005b). The progression phase is initially linear (Goss and Winkler, 1983), but decelerates to a relatively steady myopia progression and usually levels out towards a relatively stable refraction into adulthood (Flitcroft, 2014; Goss *et al.*, 1990; Goss and Winkler, 1983; Thorn *et al.*, 2005b). What triggers the sudden acceleration of myopia and what process initiates the cessation of progression is currently unknown (Flitcroft, 2014).

1.2.2.3 Age of cessation of myopia progression

Various cross-sectional studies of myopia as a function of age have shown that generally at the age of 15 to 16 years, the rate of progression of childhood-onset myopia generally shows a significant reduction or plateaus (Bucklers, 1953; Goldschmidt, 1968; Goss and Cox, 1985; Goss *et al.*, 1990; Goss *et al.*, 1985; Goss and Winkler, 1983; Rosenberg and Goldschmidt, 1981). The recent advancement in ocular biometric instrumentation has enabled more accurate data to be collected which suggest that eye growth may persist into the early 20s and possibly even in late adulthood (Dirani *et al.*, 2008).

A difference has been found in the age of cessation of myopia progression between males and females, with one study finding myopia to cease progressing one and a quarter years before it does so in males (15.25 years females, vs. 16.50 years males) (Goss and Winkler, 1983).

1.3 Ocular structural components of change during emmetropisation

1.3.1 Background

The structures of the eye grow throughout the period between birth and early adulthood. For emmetropia to be achieved and maintained despite the axial elongation of the eye, compensatory adjustments must be coordinated in other ocular structures. It is evident that coordinated growth is vital to achieving the leptokurtic distribution of adult refractive errors in which emmetropia predominates.

The manifest refractive error is the difference between the reciprocals of the focal lengths of the individual refractors of the eye, so it follows that in theory if the ocular structures grow exactly proportionally the ametropia will diminish. This is because as the AXL increases, so does the focal length of the eye, so a mismatch between the two means that refractive error becomes proportionally smaller as globe size increases. Although it is clear that proportional eye growth and scaling effects are insufficient to explain emmetropisation completely (Hoffstetter, 1969), once emmetropia is reached, proportional eye growth is likely to be instrumental in maintaining emmetropia (Mutti *et al.*, 2005).

It is thought that corneal power reduces while the crystalline lens thins and flattens during childhood, and it has been suggested that vitreous elongation is the driving force responsible for myopic shifts in refraction rather than lenticular changes (Mutti *et al.*,

2005). Though the AXL and refractive state show a leptokurtic distribution in the adult population, all other refractive components are normally distributed (Mutti *et al.*, 2005).

The cornea represents the anterior ocular refracting surface and is responsible for two-thirds of the eyes dioptric power (Gipson, 2007), with the other major refractor being the crystalline lens. The nature of the structural compensations made by both of these structures is therefore of great interest when investigating potential aetiologies of myopia.

1.3.2 Axial length

A consistent pattern in AXL change with age has not been found (Atchison *et al.*, 2008; Grosvenor, 1987b; Koretz *et al.* 1989; Leighton and Tomlinson, 1972; Ooi and Grosvenor, 1995). An increase in vitreous chamber depth is the primary correlate responsible for axial elongation in both normal emmetropisation and myopia development (McBrien and Millodot, 1987; Mutti *et al.*, 2005; Garner *et al.*, 2006, Goss *et al.*, 1997). Although excessive axial elongation seems to be the primary correlate for both early and late onset myopia (McBrien and Adams, 1997; McBrien and Millodot, 1987; Jiang and Woessner, 1996), it has been shown that there is a much wider variation in AXL for lower levels of myopia and AXL may fall within the accepted normal range for emmetropia. In these cases, it is likely that changes in the refractive structures of the eye, rather than purely axial expansion are responsible for myopia development.

Goss (1990) found that stability of axial elongation occurs earlier in myopic females (between 14.6 and 15.3 years) than in myopic males (between 15.0 and 16.7 years), which typically coincides with the end of body growth. After this age, myopic progression is typically considerably slower, however still appears to be due to vitreous chamber expansion (Lin *et al.*, 1999; McBrien and Adams, 1997).

Strang *et al.*, (1998) proposed three potential models for the nature of growth in axial myopia: Equatorial stretch, global expansion and posterior pole stretch. More recently, a fourth model has been suggested: axial expansion (Verkicharla *et al.*, 2012) (see Figure 1.5).



Figure 1.5 Current models of retinal stretching in myopia: a) global b) equatorial c) posterior polar and d) axial expansion. The solid circles represent the shape of the retina of an emmetropic eye; the dashed shapes represent the myopic retinas, and the arrows indicate the regions of stretching. Reproduced with permission (Verkicharla *et al.*, 2012) [Eye shape and retinal shape, and their relation to peripheral refraction, Verkicharla, P. K., Mathur, A., Mallen, E. A., Pope, J. M. and Atchison D. A. Ophthalmic and Physiological Optics Vol. 32, Copyright © 2012 The College of Optometrists].

In the equatorial stretching model (Figure 1.5a), the axial stretch is confined to the equatorial region of the globe. Should this be the sole mechanism for axial elongation, no anatomical changes or change in sampling density should be observable at the posterior pole. With global expansion, vitreous chamber growth is achieved by uniform expansion across the entirety of the sphere, whereas, in the posterior pole model, stretch occurs radially and is confined to the posterior pole. The axial expansion model is a combination of the equatorial and posterior pole expansion models, unlike the other three models that result in a spherical surface, axial expansion would give a prolate ellipsoid surface (Verkicharla *et al.*, 2012). For all models, there is less myopia in the periphery than the centre of the retina (relative peripheral hyperopia) as the image shell is closer to the retina in the periphery. This effect is greatest for posterior polar expansion,

followed by axial, equatorial and global expansion as seen in Figure 1.6 (Verkicharla *et al.*, 2012).

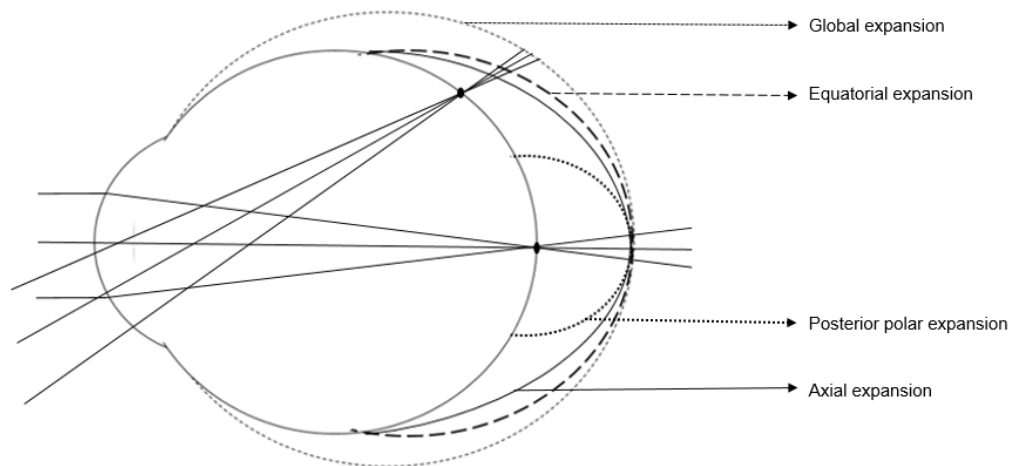


Figure 1.6 Positions of images relative to the myopic retina for the global, equatorial and posterior pole and axial expansion models. Redrawn from (Verkicharla *et al.*, 2012) [Eye shape and retinal shape, and their relation to peripheral refraction, Verkicharla, P. K., Mathur, A., Mallen, E. A., Pope, J. M. and Atchison D. A. Ophthalmic and Physiological Optics Vol. 32, Copyright © 2012 The College of Optometrists].

Atchison and colleagues (2004), considered how many of their participants fitted into each expansion model category as described in Figure 1.5, and found that no single model was sufficient to define an entire myopic population, with a quarter of myopes exclusively fitting the global expansion model, and another quarter exclusively fitting the axial expansion model. However, when vertical dimensions (height of the eye) were considered, there was a slight shift towards the global expansion model (30% of myopes fitted this model vs. 26% for axial expansion). Conversely, when considering horizontal (width) dimensions of the eye, there was a shift in favour of axial expansion, with 47% of myopes fitting this model compared to 18% showing global expansion proportions.

1.3.3 Cornea

The dioptric power of the cornea is directly related to its surface curvature. Steeper corneas have greater refractive capabilities and, therefore, result in a relatively more myopic focal point than flatter corneas. The structural changes in the cornea that have the potential to precipitate myopia are therefore important.

Interestingly, it has been shown that eyes that are axially larger generally have flatter corneas (Chang *et al.*, 2001; Grosvenor and Goss, 1998), even though myopic eyes have been found to have steeper corneas than emmetropes (Garner *et al.*, 2006; Goss *et al.*, 1997). There also seems to be meridional differences in corneal curvature in myopic eyes (Goss and Erickson, 1987), with the vertical reported as steeper than the horizontal meridian. It should be noted that this, however, is not true for late-onset myopia (Bullimore *et al.*, 1992)

It has been shown that corneal power reduces in early life, coinciding with axial elongation (Sorsby *et al.*, 1962). Mean corneal power between three and nine months of age reduces from 43.90 D to 42.83 D (Mutti *et al.*, 2005). Although the reduction in corneal power correlates with the increase in AXL, there is no significant correlation between the changes in refractive error in this period (Mutti *et al.*, 2005)

1.3.4 Crystalline lens

There is a substantial reduction in crystalline lens power during infancy (Wood *et al.*, 1996). A longitudinal study by Mutti *et al.* (2012) reported that there was a substantial inhibition of lens thinning and flattening one year before or within a year of myopia onset in children who became myopic during the study (age at baseline, six to 14 years). In this period, a reduction in refractive index and power loss of the lens was also seen. This provides further support for the notion that early-onset myopia is a product of a

breakdown in the independent relationship between lens changes and axial elongation (Mutti *et al.*, 2012). Mutti *et al.* (2012) hypothesised that hypertrophy of the ciliary muscle or cessation of scleral growth around the lens equator may be responsible for the prohibition of lens thinning and flattening.

Interestingly, it has been shown that there is a tendency for the lens to be thinner in myopic eyes than in emmetropic eyes (McBrien and Adams, 1997; McBrien and Millodot, 1987; Zadnik *et al.*, 1995), despite the breakdown in coordination between lens thinning and axial elongation. Gernet and Olbrich (1989) hypothesised that this might be due to the increased equatorial diameter in larger eyes which would result in more tension being exerted on the zonular fibres, resultantly flattening and reducing the optical power of the lens.

1.4 Why do refractive errors exist if emmetropisation occurs?

1.4.1 Background

Emmetropisation is not the sole homeostatic or disruptive process which affects eye development throughout life (Flitcroft, 2013). A child's refraction at age six can be principally attributed to their initial level of refraction at birth, and the degree of emmetropisation that has occurred in their first six years of life (Flitcroft, 2013). In order for a child to have a significant refractive error at age six, there must have been either an initial refractive error which was too high to emmetropise fully, deficient emmetropisation in spite of an initial refractive error within the normal range, or a combination of these two factors (Flitcroft, 2014). Consequently, a primary failure of emmetropisation is responsible for ametropia that is present at the age of six years (Flitcroft, 2013). However, it is clear that myopia and hyperopia follow different courses; the positively skewed distribution of refractive errors at age six suggests that most cases

of hyperopia that occur at this age are due to a failure of emmetropisation which results in persisting infantile hyperopia (Flitcroft, 2014). Conversely, the majority of cases of myopia onset after the age of six years, indicating that most cases of myopia occur in eyes that had successfully emmetropised in early life (Flitcroft, 2014). It is, therefore, clear that in most cases myopia is a result of a secondary failure of the emmetropisation mechanism to maintain the level of emmetropia or low hyperopia which it initially achieved (Flitcroft, 2014).

It is well reported that biological processes are often influenced by other random variable factors which have a probability distribution, which can be expressed at a genetic or phenotypic level (Flitcroft, 2014; Raj and Van Oudenaarden, 2008). The existence of anisometropia and refractive error variations in monozygotic twins provide evidence for the existence of such factors (Flitcroft, 2014).

The eyes of anisometropic individuals both experience the same environmental influences and the same genetics throughout life, but have different refractive errors (Flitcroft, 2014). Evidence has shown that there is a slight decline in the prevalence of anisometropia between six months and five years of age from 1.96% to 1.27% (Deng and Gwiazda, 2012). During this period, many anisometropias spontaneously resolve, and a similar number of new cases emerge (Abrahamsson *et al.*, 1990). The prevalence of anisometropia then increases up to 12 - 15 years of age to 5.77%, coinciding with the increasing variance in refractive error (Deng and Gwiazda, 2012). There is also an association between the level of ametropia and anisometropia, with an increasing frequency of anisometropia in populations with increasing refractive error, regardless of whether the refraction is myopic, hyperopic or astigmatic (Deng and Gwiazda, 2012; Qin *et al.*, 2005). The lack of close regulation of growth after the fifth to the sixth year of life, therefore, results in increased inter-subject variability as well as increased variability

between both eyes of the same subject (Flitcroft, 2014). A similar pattern has been observed in monozygotic twins, with a significant association being found between the refractive error and the degree of refractive discordance with the discordance increasing with absolute refractive error (Hammond *et al.*, 2001, Sorsby *et al.*, 1962).

1.4.2 Refractive differences in eyes with pathology

Myopia is not always an entirely benign, purely refractive condition. A study examining all children presenting to two ophthalmology departments over three years found only 8% of high myopias to be 'simple high myopia', that is, myopia associated with no ocular or systemic morbidity (Marr *et al.*, 2001). In a later study which looked at children presenting to their community optometrist or orthoptist with more than 5.00 D of myopia, 44% of myopias were associated with morbidity (Logan *et al.*, 2004a). It is clear that high myopia is associated with a high prevalence of ocular and systemic abnormalities in young children. Some children have large ametropias from birth; however, this is rare (Hiatt *et al.*, 1965), and refractive errors of this nature are often associated with genetic disorders (Marr *et al.*, 2001; Marr *et al.*, 2003). Stickler syndrome (Wilson *et al.*, 1996) and Leber's Congenital Amaurosis (Abouzeid *et al.*, 2006) are examples of conditions in which congenital and stationary ametropia has a clearly genetic basis. In conditions such as these, there seems to be a strong genetic bias away from emmetropia, and the emmetropisation mechanism generally has little effect on the large initial refractive errors (Flitcroft, 2014).

Several retinal dystrophies can be associated with myopia (Marr *et al.*, 2001). The retinal dystrophy can be stationary, as in congenital stationary night blindness, or progressive with conditions such as cone-rod dystrophy, Retinitis Pigmentosa, Bardet-Biedl syndrome and other ciliopathies. Inherited retinal dystrophies are frequently associated

with refractive errors (Chassine *et al.*, 2015). It should be noted that congenital dystrophies such as Leber's Congenital Amaurosis, are frequently linked to high hyperopias in the range of + 6.00 D to + 12.00 D, especially so in the very early forms of the condition (Hanein *et al.*, 2006). However, in retinal dystrophies that are not apparent at birth but onset in early life or later, for example, Retinitis Pigmentosa, refractive error is significantly skewed towards moderate myopia and astigmatism (Francois and Verriest, 1962). A mean spherical error of - 1.86 D has been found in a population with Retinitis Pigmentosa in comparison with + 1.00 D in a population without eye disease (Sieving and Fishman, 1978).

Clinical observations of patients with discrete central or peripheral retinal anomaly, whether this is natural or iatrogenic, provide support for the idea that peripheral visual signals can significantly influence the emmetropisation process and resultantly the genesis of central ametropia. The study of patients with peripheral pathologies such as Retinopathy of Prematurity (ROP) and Retinitis Pigmentosa has shown that in these cases larger than normal ranges of central refractive errors and, on average, more significant central refractive errors are frequently exhibited (Connolly *et al.*, 2002; Knight-Nanan and O'Keefe, 1996; Nathan *et al.*, 1985; Sieving and Fishman 1978) (See Figure 1.7). In this respect, children who have pathologies primarily affecting the peripheral retina usually exhibit larger central refractive errors than children with primarily central anomalies (Nathan *et al.*, 1985). The mechanism by which these refractive errors may be induced may be by interference from the abnormal retina with the signalling controlling emmetropisation.

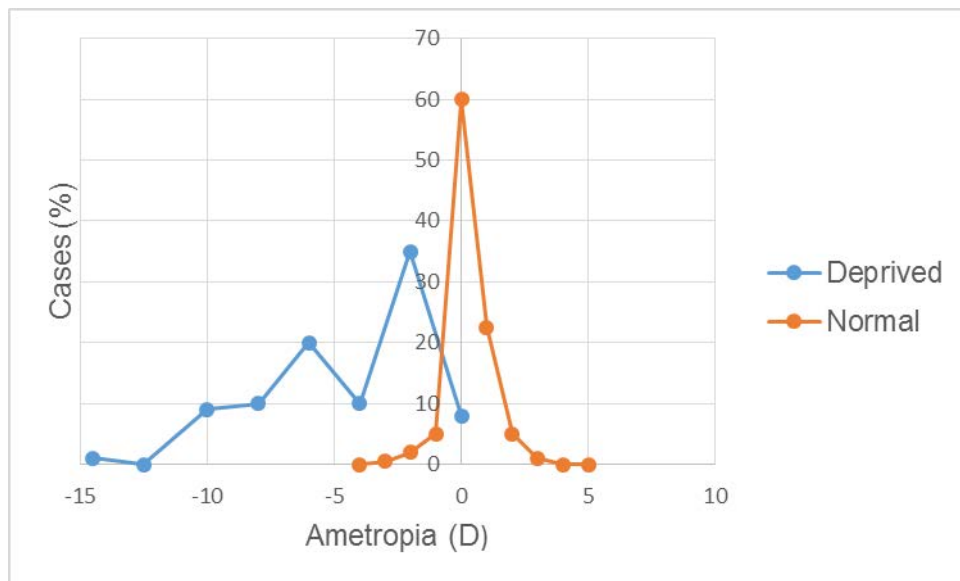


Figure 1.7 Distribution of refractive errors in healthy human eyes and eyes with ocular pathology. Redrawn from Rabin *et al.*, 1981. [Emmetropization: a vision dependent phenomenon, Rabin, J., Van Sluyters, R. C. and Malach, R. Investigative Ophthalmology and Visual Science, Vol. 20, Copyright © 1981 Association for Research in Vision and Ophthalmology Incorporated].

1.5 The current understanding of the mechanism of myopia development

1.5.1 Genetics

More than 40 genetic loci have now been associated to or linked with myopia (Zadnik *et al.*, 2015). Various twin and family studies of human refraction have also shown that myopia has some degree of heritability (Baird *et al.*, 2010). Though the exact contribution of genetic factors remains disputed, as it is likely that the interactions are polygenic and receive extremely complex input from environmental conditions.

Twin and family studies have indicated that there is a strong genetic contribution to myopia (Baird *et al.*, 2010; Hawthorne and Young, 2013; Williams *et al.*, 2013). The NICER study of 661 white Northern Irish children aged 12 to 13 identified that the children with one myopic parent were 2.91 times more likely to be myopic, with those with two myopic parents being 7.79 times more likely to be myopic than children with emmetropic

or hyperopic parents (O'Donoghue *et al.*, 2015). Nevertheless, the rapidity of the recent increase in myopia prevalence, strongly suggests that genetic variation alone is not sufficient to explain myopia genesis and that there must exist significant extraneous environmental influence (Pan *et al.*, 2015). It was traditionally thought that that high and extreme myopia may have more of a genetic basis than moderate and low myopia, which were thought to receive a higher contribution from environmental factors (Pan *et al.*, 2015). However, studies have shown that high myopia too is increasing in prevalence at a higher rate than can be explained solely by genetics (Jung *et al.*, 2012; Sun *et al.*, 2012).

1.5.2 Environmental factors

Various environmental influences have been linked to myopia in recent years. However, these are only sufficient to explain a small fraction of the variation in myopia prevalence (O'Donoghue *et al.*, 2015). Time spent outdoors has been identified as the most consistent environmental influence linked to myopia development in childhood (Jones *et al.*, 2007; Pan *et al.*, 2015; Rose *et al.*, 2008). Amongst the other potential influences are higher levels of education (Mutti *et al.*, 2002), physical activity (Jacobsen *et al.*, 2008), body stature (Dirani *et al.*, 2008), socioeconomic status (Ojaimi *et al.*, 2005; Rahi *et al.*, 2011), parental smoking (Stone *et al.*, 2006), birth order (Rudnicka *et al.*, 2008) and parental education level (Rudnicka *et al.*, 2008). It should be noted that equivocal data have been published on other risk factors including breastfeeding status (Chong *et al.*, 2005; Rudnicka *et al.*, 2008) and time spent performing near work (Ip *et al.*, 2008; Mutti *et al.*, 2002; Saw *et al.*, 2002).

1.5.3 Deprivation myopia

Form deprivation myopia has been experimentally induced in animal models by neonatal lid suturing (Sherman *et al.*, 1977; Wallman *et al.*, 1978; Wiesel and Raviola, 1977; Yinon, 1980), corneal opacification (Wiesel and Raviola, 1979), and the use of pattern vision attenuating occluders (Wallman *et al.*, 1978). Induced myopia, however, fails to occur in dark reared, lid-fused monkeys (Raviola and Wiesel, 1978). It follows that it is not deprivation alone, but exposure to anomalous patterned stimuli that is a precipitant of myopia, at least in an animal model.

In contrast to the conclusions of the above animal models, O'Leary and Millodot (1979) studied humans with early onset ptosis. Similarly, there was an increased incidence of myopia in ptotic eyes. However, this was not consistently associated with amblyopia. It was therefore concluded that it is partial or full occlusion that causes myopia in these individuals rather than attenuated pattern vision.

Rabin *et al.* (1981) investigated emmetropisation in humans with ocular pathologies known to disrupt pattern vision in early life. There was a significant increase in the incidence of myopia in subjects with both bilateral and unilateral ocular anomalies, regardless of the underlying pathology. Bilateral pathologies were: congenital cataract, optic atrophy, macular dystrophy and retrolental fibroplasia. Unilateral anomalies were: Retrolental fibroplasia, persistent pupillary membrane, vitreous debris, ptosis with and without lens opacity, trauma and traumatic cataract. Although it is possible that there is an innate disease process in all of these pathologies that cause myopia, it seems more reasonable to suggest that regardless of the aetiology behind the disruption to form vision, prolonged exposure to pattern blur in infancy can induce myopia through the disruption of emmetropisation.

1.6 Myopia induced with refractive lenses

1.6.1 Background

The exact mechanism by which the eye develops and emmetropises is not fully understood (Mutti *et al.*, 2005). The compensatory changes in the lens and cornea which were discussed in the previous chapter clearly indicate that passivity is an important feature of the emmetropisation process (Mutti *et al.*, 2005), and that at least part of the developmental drift in refractive error towards emmetropia can be attributed to a simple optical artefact of eye growth (Wildsoet, 1997).

However, the correlation of the various ocular components cannot be explained solely in terms of genetics and the physical characteristics of the growing eye. The passive nature of these factors would imply that clinical manipulations, for example of spectacle lens power are unlikely to influence refractive outcomes (Wildsoet, 1997). Nevertheless, accumulating data from animal studies of myopia and visual deprivation on eye growth have indicated that emmetropisation has a strong, active component, which is guided by visual experience and feedback (Irving *et al.*, 1992; Schaeffel *et al.*, 1988; Smith *et al.*, 1999; Wallman *et al.*, 1995; Wildsoet, 1997). However, the question of what the mechanism for feedback is and to what extent passive features such as genetic control are relied upon remains largely unanswered (Trolie, 1992).

Central to the visual feedback model is the assumption that defocus is able to modulate eye growth to decrease refractive error during emmetropisation (Mutti *et al.*, 2005). A number of experimental paradigms have been applied to a wide range of species, and they have revealed that altered retinal image quality is the primary aetiological candidate for the onset and development of myopia as it can lead to consistent and predictable changes in eye development (Read *et al.*, 2010). It is clear that emmetropisation does

contain an active component that is vision dependent, and that altered visual experience can induce myopia (Irving *et al.*, 1992; Schaeffel *et al.*, 1988; Smith *et al.*, 1999; Wallman *et al.*, 1995; Wildsoet, 1997).

Animal models making specific experimental manipulations to deprive the eye of clear form vision during early development in the absence of pathologically induced image degradation have induced predictable compensatory ocular structural change, altering emmetropisation (Sivak *et al.*, 2012). In these cases, the myopia is precipitated as a result of both spatial form deprivation and induced hyperopic defocus.

1.6.2 Myopia induced with refractive lenses

Compensatory growth due to induced optical defocus was first demonstrated in the monkey model of Wiesel and Raviola (1977) and the young chick model of Wallman and colleagues (1978), where modest environmental manipulation resulted in marked myopia. It has since been shown that ocular growth can be tuned to the sign and power of lenses simulating refractive errors (Schaeffel *et al.*, 1988). While many experiments investigating the development of refractive error are performed on chick eyes, various other mammalian and avian models have been studied (Sivak *et al.*, 2012). Form deprivation myopia has also been shown to occur in another bird, the American Kestrel (Anderson *et al.*, 1992), as well as tree shrews (Marsh-Tootle and Norton, 1989), guinea pigs (Howlett and McFadden, 2006; Ouyang *et al.*, 2003), grey squirrels (McBrien *et al.*, 1993), mice (Tejedor and de la Villa, 2003), cats (Kirby *et al.*, 1982) and primates (Hung *et al.*, 1995; Smith, 2013a; Smith 2013b; Wallman *et al.*, 1978).

Form deprivation generally induces myopia (Sivak *et al.*, 2012). Schaeffel and colleagues' 1988 study showed that both myopia and hyperopia could be induced by using either concave or convex lenses to alter the retinal image. Other studies have further

demonstrated that a wide range of refractions can be induced with the use of refractive spectacle lenses and goggles (Irving *et al.*, 1991; Irving *et al.*, 1995). In short, induced hyperopic defocus (simulated with the use of concave lenses) acts as a stimulus for axial elongation and, as a result, the eye is myopic when the lens is removed (Sivak *et al.*, 2012). Conversely, under conditions of myopic defocus (induced by the use of convex lenses) there is an inhibition of ocular growth (Liu and Wildsoet, 2011). It is likely that this occurs via some form of homeostatic feedback system whereby the eye either grows or does not grow to keep the retinal plane as close to the focal position of the image as possible (Sivak *et al.*, 2012). Zhu and colleagues (2005) have shown that in chick eyes, compensatory ocular changes occur within one to two hours of the introduction of both positive and negative lenses.

There has been varied data on whether there is complete refractive compensation. Irving *et al.* (1992), noted that in a chick model the compensatory response exactly matched the degree of lens-induced defocus, for the range - 10.00 D to + 15.00 D. Compensation did not occur to the same extent as in the earlier study by Schaeffel *et al.* (1988). Differences in the chick breed and the age of exposure to the blur condition may explain this disparity.

Smith (2008) systematically induced varying degrees of hyperopic and myopic retinal blur in monkeys with the use of divergent and convergent optical lenses (see Figure 1.8).



Figure 1.8 Graphs showing the age of the monkey against refractive error, under differing lens conditions, with data from Hung *et al.*, 1995. Reproduced with permission (Smith, 1998) [Spectacle lenses and emmetropization: the role of optical defocus in regular ocular development, Smith, E. L. 3rd. Optometry and Vision Science Vol. 75, Copyright © 1998 American Academy of Optometry].

The research was conclusive in showing that ocular growth can be manipulated predictably and proportionally according to the severity of induced blur. + 3.00 D, + 6.00 D and + 9.00 D lenses all inhibited axial elongation, with the effect being markedly enhanced at each higher diopetre trial (increased myopic blur). Predictably, divergent lenses of - 3.00 D, and - 6.00 D both induced significant axial elongation, with the higher-powered lens showing a more marked effect. Though entire visual recovery occurs after

the removal of convergent lenses, myopia remained after exposure to negative lenses. However, some recovery was evident.

It has been shown that recovery from form deprivation myopia occurs by a relative slowing of the rate of vitreous chamber elongation, while the other ocular components continue to grow as normal (McBrien *et al.*, 2000; Wallman and Adams, 1987) the net result is a relative increase in hyperopia (reduction in myopia). Modulation of choroidal thickness has also been implicated in chick eyes (Wallman *et al.*, 1995) and monkeys (Hung *et al.*, 2000).

1.6.3 Understanding of the mechanism for detecting defocus

As it is apparent that optical blur affects growth, it follows that there must be a mechanism that can detect the sign of defocus, for the appropriately modified axial growth to occur. Ascertaining the nature and characteristics of such a mechanism is crucial in further understanding emmetropisation (Schaeffel and Wildsoet, 2013). It is also important to localise the mechanism. However, data remains equivocal on whether the retina itself contains the machinery to process images to determine the sign of defocus, or whether it receives cerebral input from higher centres in the visual pathway (Schaeffel and Wildsoet, 2013).

As discussed previously (see Sections 1.4.2 and 1.6.2), it is known that both experimental (Sherman *et al.*, 1977; Wallman *et al.*, 1978; Wiesel and Raviola, 1977; Wiesel and Raviola, 1979; Yinon, 1980) and pathological (Rabin *et al.*, 1981) optical image degradation leads to excessive axial elongation. But, this does not occur in cases of induced myopic defocus, where the degraded image falls anterior to the retina – at least in animal models. Thus, it is apparent that deprivation myopia cannot be the sole

mechanism for uncoordinated ocular growth, as there is clearly a way to recognise the location of blur relative to the photoreceptor layer.

Optic nerve section studies in animals support the theory that the retina has, at least, the complete machinery to convert image features into growth signals (Schaeffel and Wildsoet, 2013; Trolie and Wallman, 1991). The development of form deprivation myopia continues post optic nerve section (Norton *et al.*, 1994; Trolie *et al.* 1987; Wildsoet and Pettigrew, 1988). In chicks, the eye is able to distinguish whether the input visual signal is over or under-focused and in chicks at least, rapidly adjusts the retinal position and therefore the focal length of the eye, by altering the thickness of the choroid accordingly (Wallman *et al.*, 1995). The rate of ocular growth then either accelerates or slows down resulting in a more permanent change in refractive state, subsequently ending up in an eye that is either too long or too short (Sivak *et al.*, 2012). However, myopia does not develop in response to negative lenses (Wildsoet and Wallman, 1995). Wildsoet and Wallman (1995) state that this suggests that compensation for hyperopic defocus requires the central nervous system.

Thus, it seems that both retinal and central elements are involved in the normal active feedback process of emmetropisation and that the retina must be able to provide some biochemical signal as a response to local defocus, which controls eye growth, (Wallman and Winawer, 2004).

However, it is clear that observations from animal studies cannot always be applied to human refractive development. Though data from chicken models strongly suggests that the retina can determine the sign of induced defocus, this does not always appear to be true according to findings from studies of human subjects. For example, should an image focused on the vitreal side of the retina be a cue for the inhibition of axial elongation, under-correction should be an effective modality for myopia control (Schaeffel and

Wildsoet, 2013). However, this does not seem to be the case in humans (Chung *et al.*, 2011). It has been suggested that perhaps the accommodation system becomes 'lazy' during under-correction causing the focal plane to shift in the opposite direction during near work (Schaeffel and Wildsoet, 2013). Similarly, the same theory should be applicable to uncorrected myopia, which according to this thinking should be a self-limiting condition, but is clearly not (Schaeffel and Wildsoet, 2013). Accommodation inaccuracy in myopes has also been implicated, as studies have found that accommodation is less accurate than in emmetropes (Gwiazda *et al.* 1995; Gwiazda *et al.* 1993; Mutti *et al.*, 2006), perhaps because myopes have a higher tolerance to incorrectly focussed images (Abbott *et al.*, 1998). Consequently, accommodation may be too weak during reading, which could stimulate more axial growth, despite the eye already being myopic (Schaeffel and Wildsoet, 2013).

1.7 Peripheral image focus and refraction

1.7.1 Introduction

The human reliance on macular vision has long led to the assumption that defocus signals corresponding to foveal vision are the prevailing force governing the emmetropisation process and in cases of its failure, the precipitation of ametropia (Verkicharla *et al.*, 2012). Due to the relative vastness of the peripheral retina and the quantity of photoreceptors compared to the discrete foveal zone, it seems reasonable to suggest that the contribution of the peripheral retina should not be discounted. Experimental animal models published in the 1970s have helped to promote further understanding by legitimising the study of the relationship between environmental factors and the refractive development of the eye (Sivak *et al.*, 2012).

It has long been hypothesised that the state of image focus on the peripheral retina may have the potential to affect refractive development (Sivak *et al.*, 2012). It is known that retinal quality (Jennings and Charman, 1981; Navarro, 1993) and spatial resolution (Weymouth, 1958) reduces as a function of increasing retinal eccentricity. Nevertheless, avian studies have shown that even when only very low spatial frequency information is available, the sign of defocus remains detectable, and consequently appropriate ocular growth towards emmetropia can be coordinated (Schaeffel and Diether, 1999). Furthermore, Wallman and Winawer (2004) indicated that the defocus signal in the periphery of the retina should be stronger than at the retina owing to the fact that there are more neurones in that region. Similarly, Ho and colleagues (2012) found that the human retina has an electrical response which is sensitive to defocus and that the paracentral retina has a more vigorous response to optical defocus than is seen at the central retina.

1.7.2 Animal studies

Animal studies of myopia development have provided mounting evidence to suggest the existence of a mutually dependent relationship between central and peripheral retinal signalling (Huang *et al.*, 2009; Smith *et al.*, 2009; Smith *et al.*, 2005; Wallman *et al.*, 1987). They also show the significant contribution made by the peripheral retina to emmetropisation and the development of ametropia resulting from abnormal visual experience (Smith *et al.*, 2005).

In chicks (Diether and Schaeffel, 1997; Miles and Wallman, 1990) and primates (Smith *et al.*, 2009; Smith *et al.*, 2010), hemifield form deprivation results in excessive eye growth localised to the affected area only. Further evidence comes from the Smith *et al.* (2005; 2007) studies with primate models where visual input is altered in discrete retinal

locations. In Smith *et al.*'s 2005 experiment, a translucent goggle with a central aperture deprived the peripheral retina alone of form vision. Regardless of the fact that central vision was unrestricted, eyes under these conditions developed form deprivation myopia to a comparable extent to those in which vision in the entirety of the visual field was disrupted. Smith *et al.*'s following experiment (2007) disrupted the central retina exclusively, by rendering it non-functional by thermal laser ablation. Under these conditions, emmetropisation was either unaffected or form deprivation myopia developed. However, in cases where form deprivation myopia occurred, the eyes recovered comparably to intact eyes, despite the non-functionality of the fovea. This research is crucial in indicating that foveal signals do not appear to be essential for many aspects of vision-dependent ocular development; that peripheral visual signals can, in isolation exert control over refractive development; and that, in cases of conflicting visual signals from the retinal centre and periphery, the peripheral retinal signals can dominate central development and ocular growth (Sankaridurg *et al.*, 2011).

Animal studies have led to the widely accepted understanding that hyperopic defocus caused by hyperopia in infancy can modulate the growth of the eye to reduce refractive error (Smith *et al.*, 1999; Wildsoet, 1997). The mechanism by which this occurs is thought to be that hyperopic images falling behind the retina cause the eye to elongate towards the hyperopic focal plane in an attempt to gain an clear image, and consequently, hyperopia reduces. In more recent years, off-axis refractive error has been called into question as being critical in emmetropisation, the notion being that peripheral hyperopic image shells can independently drive central growth, in turn leading to myopic ametropia (Smith *et al.*, 2007).

1.7.3 Relative peripheral hyperopia

Studies that have cited relative peripheral hyperopia as important in myopia development do so on the basis that hyperopia reflects the relatively more prolate shape of myopic eyes, in which the AXL exceeds the equatorial diameter (Yamaguchi *et al.*, 2013). Human myopia has been associated with relatively prolate globe shapes (Mutti *et al.*, 2000). Consequently, post refractive correction when the visual image is optimally focussed on the fovea, the image shell falls posterior to the retina in peripheral locations (see Figure 1.9). The defocus induced in the periphery is termed 'relative peripheral hyperopia'. Consequently, an emmetropic eye with a steeper retina or an already myopic eye may elongate causing myopia, as a response to the induced peripheral hyperopic defocus.

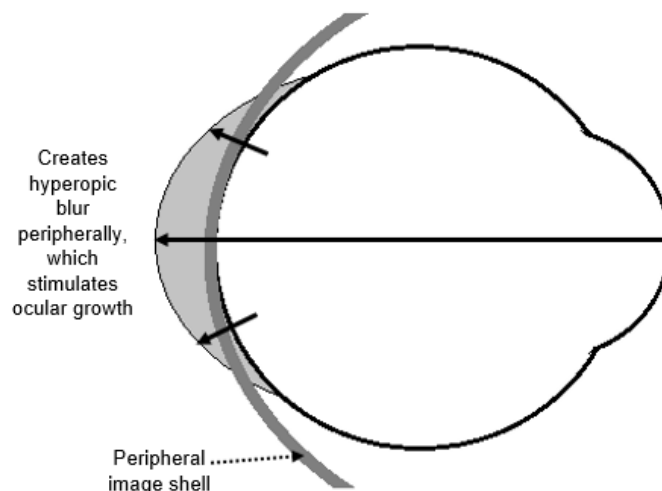


Figure 1.9 Schematic diagram to illustrate the hypothesis that peripheral hyperopic blur may act as a stimulus for axial expansion of the eye as the eye grows towards the position of the peripheral image shell.

However, this model is known to be over-simplified as eyes are rarely rotationally symmetric (Verkicharla *et al.*, 2012). Therefore, the peripheral refraction varies in different meridians of the visual field (Verkicharla *et al.*, 2012). Additionally, rather than being generally spherical, the majority of emmetropic eyes demonstrate low levels of

peripheral myopia, and most emmetropic retinas are oblate in shape rather than spherical (Atchison *et al.*, 2005a).

The pencil of light coming from an off-axis object point on a plane surface, passing through a symmetrical optical system does not come to a point focus, but instead is focussed as lines at two positions (Verkicharla *et al.*, 2012). One of these lines corresponds to the light which is refracted in the plane which contains the object point and the optical axis (the tangential plane) while the other corresponds to the plane perpendicular to this (the sagittal plane) (Verkicharla *et al.*, 2012). For a range of object points across the surface, there will be two image shells formed as seen in Figure 1.10a. Should the shape of the retina influence growth, it will be by summation of signals across the retina, not merely at a single position (Verkicharla *et al.*, 2012).



Figure 1.10 a) formation of tangential (T-dotted line) and sagittal (S-dashed line) images either side of the retina (R-bold line). b) Formation of the mean of the image shells and its location relative to the retina for three different retinal shapes. Reproduced with permission (Verkicharla *et al.*, 2012) [Eye shape and retinal shape, and their relation to peripheral refraction, Verkicharla, P. K., Mathur, A., Mallen, E. A., Pope, J. M. and Atchison D. A. Ophthalmic and Physiological Optics Vol. 32, Copyright © 2012 The College of Optometrists].

For an emmetropic eye with the assumed 'normal' retinal shape of a sphere with a 12 mm radius of curvature, the image shell corresponding to the average of the tangential

and sagittal image shells (far-point sphere) would coincide approximately with the retinal sphere (Verkicharla *et al.*, 2012). However, the retinal sphere and mean far-point sphere will no longer coincide in emmetropic eyes with other retinal curvatures, this can be seen in Figure 1.10b. Light from a distance off-axis location still coincides with the 'normal' retinal position, resulting in relative peripheral myopia for flatter retinas, and conversely relative peripheral hyperopia for steeper retinas. This can also be applied to myopic eyes, assuming that the optics are the same besides the longer AXL (Verkicharla *et al.*, 2012).

1.7.4 Human peripheral refraction

The peripheral refraction of the eye has been investigated since the investigations of Thomas Young (Young, 1801) and has recently made a resurgence as a topic of great interest due to the current focus on the possible roles of eye shape and peripheral refraction in refractive development.

In the 1930s, the work of Ferree and colleagues examined the peripheral refraction of 21 subjects, using an objective refractometer in the horizontal plane to an eccentricity of 60° (Ferree and Rand, 1933; Ferree *et al.*, 1931; Ferree *et al.*, 1932). Three distinct 'types' of peripheral refraction pattern were identified. Two further patterns were identified in a later work by Rempt *et al.* (1971). Descriptions of each type are shown in Table 1.3.


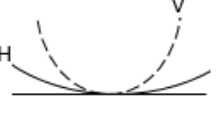
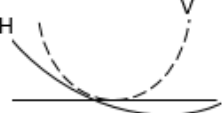
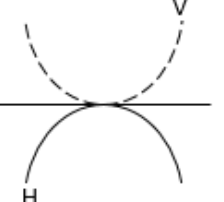

Name given to peripheral refraction pattern		Tangential refraction (along horizontal meridian)	Sagittal Refraction (along vertical meridian)	Skiagram
Ferec <i>et al.</i> , 1931	Rempt <i>et al.</i> , 1971			
Type B	Type I	Becomes more hyperopic	Becomes more hyperopic	
	Type II	Becomes more hyperopic	Becomes more hyperopic	
Type C	Type III	Asymmetrical astigmatism – peripheral refraction differs between the nasal and temporal sides of the peripheral field	Becomes more hyperopic	
Type A	Type IV	Becomes more myopic	Becomes more hyperopic	
	Type V	Becomes more myopic	Becomes more myopic	

Table 1.3 Five types of skiagrams (peripheral refraction plots) described by Ferree *et al.*, 1931, and Rempt *et al.*, 1971. The curves are shown as parabolas, but real plots are seldom as regular. For all graphs, visual field position is represented on the x-axis and refraction on the y-axis. Skiagrams redrawn from (Verkicha *et al.*, 2012) [Eye shape and retinal shape, and their relation to peripheral refraction, Verkicha, P. K., Mathur, A., Mallen, E. A., Pope, J. M. and Atchison D. A. Ophthalmic and Physiological Optics Vol. 32, Copyright © 2012 The College of Optometrists].

1.7.5 Models of shape and their relation to peripheral refraction

It is likely that eye shape, retinal shape and peripheral refraction are related (Verkicharla *et al.*, 2012). However, Verkicharla and colleagues (2012) suggest that the true picture is often over-simplified due to unwarranted linking of the concepts. For example, a specific shape of the eye is taken to infer a particular pattern of refraction such as a prolate shape causes relative peripheral hyperopia or vice versa (Verkicharla *et al.*, 2012). In a similar way, retinal shape may be interchanged with the more nebulous concept of eye shape. Owing to this, the large variation in measures of peripheral refraction and the fact that the eye's optics, not retinal shape alone contribute to peripheral refraction, Verkicharla and colleagues (2012) recommend great caution is taken when using and interpreting these relative quantities.

Peripheral refraction studies have typically concluded that myopic eyes appear to be prolate or less oblate in shape than emmetropic and hyperopic eyes (Logan *et al.*, 2004b), while Atchison *et al.* (2005a) found that the retina itself while showing the same trend remains oblate in shape for myopic eyes though to a lesser degree than in emmetropia (discounting high myopia). A recent study using T2 weighted MRI by Gilmartin *et al.* (2013) concluded that prolate ellipse posterior chamber shapes were rarely found in subjects with myopia. It was hypothesised that this is likely to be because axial elongation is attenuated if the shape of post-equatorial regions of the posterior chamber approaches a spherical shape. This spherical shape may act as a biomechanical limitation to further axial elongation in myopia (Gilmartin *et al.*, 2013). It was further added that prolate ellipse shapes of the posterior chamber, may therefore only occur in eyes with very high degrees of myopia and associated pathological changes (Gilmartin *et al.*, 2013). It has also been hypothesised that the expansion of the retina is dictated by the size of the orbit owing to the posterior section of the eye having

least restraint from the orbital walls and, therefore, allowing it to grow more than any other parameter (Atchison *et al.*, 2005a).

Atchison and colleagues' 2004 study compared the ocular dimensions of 88 participants aged between 18 and 36 years (cornea to retina AXL, height and width) and were able to associate ocular shape with refractive error. Although there was significant variation between participants, myopic eyes were found to be larger in all respects than emmetropic and hyperopic eyes. This was particularly pronounced for AXL measures (Atchison *et al.*, 2004). Atchison and colleagues' later (2006) study went on to look at peripheral refraction readings taken in both the vertical and horizontal meridians. Myopia was found to have a more pronounced effect in the horizontal aspect of the periphery than in the vertical direction. This is consistent with the current understanding of the shape of myopic eyes (Atchison *et al.*, 2004; Atchison *et al.*, 2005; Atchison *et al.*, 2006). The models of Charman and Jennings (1982) and Dunne *et al.* (1987) can largely explain the myopic shifts in peripheral refraction in emmetropes turning to relative hyperopic peripheral shifts in refraction in myopic subjects along the horizontal field (Atchison *et al.*, 2006). These models work on the assumption that the retinal equator stays the same distance from the visual axis as myopia increases (Charman and Jennings, 1982; Dunne *et al.*, 1987). However, the eye is known to increase in size horizontally, vertically and axially in myopia (Atchison *et al.*, 2004; Atchison *et al.*, 2005a). As this increase is asymmetric, and much more marked in the vertical than horizontal direction, the retina will be flatter along the vertical than the horizontal meridian, thus reducing the tendency for relative peripheral hyperopia vertically as central myopia advances (Atchison *et al.*, 2006).

The Orinda Longitudinal study of myopia (Mutti *et al.*, 2000) measured refraction centrally and 30° nasally, in a cohort of 822 children aged between five and 14 years. Relative

peripheral myopia was found in both emmetropic and hyperopic cohorts though this was more marked in the hyperopic subjects. It was suggested that this demonstrates an oblate shape. Conversely, myopic participants demonstrated relative peripheral hyperopia, and it was suggested that this was a sign of a relatively prolate ocular shape.

Sng *et al.* (2011a) measured peripheral refraction at 15 and 30 degrees either side of fixation in 250 Singaporean children aged between three and 15 years. While children with moderate and high myopia (≤ -3.00 D) displayed relative peripheral hyperopia at all eccentricities, those with low central myopia (-0.50 D to -2.99 D) only showed relative peripheral hyperopia at 30 degrees not at 15 degrees. Relative peripheral myopia was present for emmetropes and hyperopes at both eccentricities. Calver *et al.* (2007) examined peripheral refraction measurements at 10, 20 and 30 degrees from fixation in emmetropic and myopic adults. A significant difference between emmetropes and myopes was only found at 30 degrees in the temporal retina. In contrast to the work of Sng *et al.* (2011a) when mean spherical refractive error was considered, myopes did not show a change in peripheral refraction, although emmetropes did become more myopic in the periphery. Owing to these findings, Calver *et al.* (2007) concluded that myopia did not appear to be associated with changes in peripheral refraction during distance or near vision.

1.7.6 Peripheral refraction and progression of myopia

In 1971, a study followed the refraction of 214 trainee pilots over an unspecified number of years suggested that peripheral refractive state may be an indicator for as well as a precipitant of myopia (Hoogerheide *et al.*, 1971). Candidates with hyperopic peripheral refractive errors with the type I profile (see Table 1.3) on enrolment on the course were more predisposed to develop myopia over the following few years than those with initially

emmetropic or myopic peripheral refractive errors. The proportions in each refractive profile group who eventually developed myopia were as follows: type I 47%, type II 7%, type III 21%, type IV 3% and type V 0% (Hoogerheide *et al.*, 1971).

The studies of Stone and Flitcroft (2004), and Wallman and Winawer (2004) revisited the work of Hoogerheide *et al.* (1971), gaining momentum for the consideration of peripheral optics as being able to influence the development of myopia either due to peripheral refraction or retinal shape. However, a review of Hoogerheide and colleagues 1971 work and Rempt and colleagues 1971 work by Rosen and colleagues (2012) questions the suggestion that peripheral refractive error can be used as a predictor for myopia on the grounds that these works have been misinterpreted since publication. Rosen *et al.* suggested that the peripheral hyperopia data which is presented may have been taken following the development of ametropia and consequently cannot be used when determining myopia indicators (Rosen *et al.*, 2012).

Studies have found that age (Atchison *et al.*, 2005b; Chen *et al.*, 2010) and ethnicity (Kang *et al.*, 2010) have no real effect on peripheral refraction patterns. A number of studies have found emmetropic individuals to have a weak relative peripheral myopia (Atchison *et al.*, 2006; Chen *et al.*, 2010; Kang *et al.*, 2010; Mutti *et al.*, 2000), although some have found a weak tendency towards hyperopia in either one or both sides of the visual field (Millodot, 1981). A study of emmetropic eyes also noted that some individuals shift from a relative peripheral myopic pattern at angles over 45 degrees to a hyperopic pattern (Gustafsson *et al.*, 2001). Hyperopic groups have been found to have relative peripheral myopia (Atchison *et al.*, 2005b; Millodot, 1981). Other studies of human children and young adults have also concluded that myopic eyes exhibit relative peripheral hyperopia (Atchison *et al.*, 2006; Berntsen *et al.*, 2010; Chen *et al.*, 2010; Kang *et al.*, 2010; Millodot, 1981; Mutti *et al.*, 2000; Radhakrishnan *et al.*, 2013:

Yamaguchi *et al.*, 2013). It has been shown that to some extent, the degree of relative peripheral hyperopia increases according to the degree of myopic ametropia (Atchison *et al.*, 2006). Atchison and colleagues (2006) also found that peripheral astigmatism decreases with increasing myopia.

Moreover, a longitudinal study examining the eyes of 979 children, of whom 605 became myopic, concluded that relative peripheral hyperopia can be an important predictor of the onset and the future development of myopia in children (Mutti *et al.*, 2007). However, in 2011, the works of Mutti *et al.* (a continuation of the group's 2007 study) evaluated that over time, the state of peripheral refraction in children, did not, in the end, have a consistent influence on myopia development. There was found to be a mean annual progression of myopia of only - 0.024 D per dioptre of relative peripheral hyperopia (Mutti *et al.*, 2011). In the same year, Sng and colleagues (2011) carried out a one-year longitudinal study of Chinese Singaporean children aged four to ten years and found that baseline peripheral refractions were similar for children regardless of whether they became myopic during the study or not. On follow - up, the children who were myopic at baseline or became myopic over the duration of the study had relative peripheral hyperopia, whereas children who did not become myopic retained relative peripheral myopia. It was concluded that these results indicate that relative peripheral hyperopia might not be an essential factor in myopia development. Furthermore, Charman and Radhadkrishnan (2010) had previously suggested that in cases where relative peripheral hyperopia is associated with the onset of myopia, rather than being a causative factor, it may simply be a consequence of the development of myopia. In this paper, Charman and Radhadkrishnan (2010) also discussed the work of Logan *et al.* (2004b) which suggested that eye shape in people of Chinese origin is more axially symmetric than in Caucasian eyes - owing to this, they drew the conclusion that the state of peripheral refraction may not be associated with the development of myopia in all ethnic groups.

Understanding of the role that the peripheral defocus plays in human myopia development has become increasingly important with the increasing prevalence of the condition. Recent efforts have addressed the question of whether peripheral refraction could be exploited to reduce myopia progression in children (Sivak *et al.*, 2012). Smith and colleagues (2005) suggested that altering peripheral retinal image quality may be exploited as a treatment modality to control eye growth and affect the refractive development of the eye.

The results of recent clinical trials involving children with myopia have indicated that both myopia progression and AXL elongation can be slowed with the use of lenses that introduce more positive power in the periphery (Sivak *et al.*, 2012). The work of Sankaridurg *et al.* (2010) compared three different specialised spectacle lens designs and one single-vision, control, spectacle lens, worn by 210 Chinese children aged six to 16 years old, over a period of one year, with the intention of reducing defocus on the peripheral retina. Lens one was rotationally symmetric, with a clear, 20 mm central zone and a ramped treatment zone in the periphery with an increasing positive power up to + 1.00 D at 25 mm. Lens two was of a similar design but with a 14 mm central zone and + 2.00 D addition in the periphery. Lens three was an aspheric design, with a clear central zone which extended 10 mm inferiorly, nasally and temporally from the centre. The intention of this lens design was to reduce astigmatism in the horizontal meridian, while simultaneously inducing + 1.90 D of additional peripheral plus, 25 mm from the centre. Though no significant reduction in myopia progression was found for any of the lens types, a minimal reduction in myopia progression (0.29 D, $p = 0.004$) could be made in children less than 12 years old with myopic parents and wore the type three lens (Sankaridurg *et al.*, 2010).

Later studies have examined the use of multifocal contact lenses, anticipating that they may yield more marked results owing to them remaining properly aligned on the eye regardless of ocular movement (Sivak *et al.*, 2012). Anstice and Phillips (2011) fitted 40 children of multi-ethnic backgrounds with contact lenses which were specifically designed to be an intervention to limit the progression of myopia. These soft contact lenses had a central distance correction zone and concentric peripheral treatment zones containing a + 2.00 D addition, intended to impose simultaneous peripheral myopic defocus when the child is viewing both distance or near targets. The lenses were worn in one eye for the first ten-month phase before being swapped to the other eye for the following ten months. Myopia progression was reduced by 30% in 70% of the children wearing the test lens. It was, therefore, concluded that the approach of inducing continuous myopic defocus alongside simultaneous clear images can affect central ametropia and significantly reduce the rate of myopia progression (Anstice and Phillips, 2011).

Similar findings were also made in a study examining the use of multifocal contact lenses with a central clear zone with progressing positive power in the periphery (+ 1.00 D addition at 2 mm, increasing to + 2.00 D at the edge of the 9 mm treatment zone) in a 12 month study of 45 Chinese children (Sankaridurg *et al.*, 2011). Compared to 40 children in the control group who wore conventional sphero-cylindrical spectacle lenses, the 45 children wearing the test contact lens showed less progression in myopia (- 0.57 D vs. - 0.86 D).

A more recent study (Lam *et al.*, 2014) assessed a 'Defocus Incorporated Soft Contact' (DISC) contact lens. This lens was a concentric ring design similar to that used in Anstice and Phillips' 2011 study, however, it incorporated a positive addition of + 2.50 D, + 0.50 D stronger than the earlier study. In this study, 221 children aged eight to 13 years

wore either the DISC lens or single vision contact lenses. At study completion, the DISC group were found to have a reduction in myopia progression of 25%, with a correlated reduction in axial elongation (Lam *et al.*, 2014).

It is not just custom designed contact lenses designed for the sole purpose of myopia control which have been used in such studies. Commercially available centre-distance multifocal contact lenses (Proclear Multifocal 'D'; CooperVision, Fairport, New York) were fitted to 40 myopic children aged eight to 11 years (Walline *et al.*, 2013). After two years of wearing the lenses, myopic progression was reduced by 50% and AXL elongation by 29% in these children compared to children who wore single vision contact lenses.

1.8 Other influences on myopia development

1.8.1 The role of the sclera and choroid in growth regulation

The aetiological link between the choroid and sclera is currently receiving much interest as it has been found that defocus can affect both choroidal thickness and scleral growth rate in humans (Read *et al.*, 2010). Choroidal thickness changes in response to defocus have been demonstrated in both chick (Wallman *et al.*, 1995) and primate (Hung *et al.*, 2000) models. Defocus elicits a choroidal response within minutes of exposure, but this always precedes the subsequent growth change mediated by the sclera (Read *et al.*, 2010). Transient changes in choroidal thickness have been shown to be mechanistically linked to the scleral synthesis of macromolecules and thus, have an important role in the homeostatic control of eye growth in myopia (Nickla and Wallman, 2010). Hyperopic retinal defocus promotes a thinning of the choroid and an increase in scleral growth rate, both resulting in a posterior movement of the retina towards the focal plane. Conversely, myopic defocus causes choroidal thickening and slows scleral growth, leading to an

anterior movement of the retina. A work by Read *et al.* (2010) was the first to investigate whether these choroidal responses to sustained blur exist in the human eye. Small increases in AXL were observed in response to hyperopic defocus and small decreases were found with imposed myopic defocus. Diffuse defocus lead to a small increase in AXL. These changes were found to occur by 60 minutes of exposure. Read *et al.* concluded that the bidirectional nature of the changes observed suggests that the human visual system is able to detect the presence and the sign of defocus and alter AXL accordingly (Read *et al.*, 2010).

1.8.2 Dysfunction of the ciliary apparatus and near induced transient myopia

Without the ciliary apparatus, the eye would be unable to exert any lenticular accommodative response. It is a long-standing observation that sustained, excessive and high cognitive demand near work may cause myopia (Angle and Wissman, 1980; Richler and Bear, 1980; Rosenfield and Gilmartin, 1998; Zadnik *et al.*, 1994). To date, no consistent link between myopia and near work has been established, however, malfunctions of accommodation have been implicated (Allen and O'Leary, 2006). It has been suggested that this may result from a dysfunction of the ciliary body following cessation of sustained near vision (near induced transient myopia) and collaterally, a dysfunction of the accommodative response (lag of accommodation) (Ciuffreda and Vasudevan, 2008; Vera-Díaz *et al.*, 2002; Wolffsohn *et al.*, 2003a; Wolffsohn *et al.*, 2003b). There are some ramifications of dysfunction that affects retinal image quality via accommodation and or oculomotor control. Anatomical studies have shown that the choroid and ciliary muscle may be continuous, forming a smooth muscle layer that encapsulates the entire eye (van Alphen, 1986). It has followed that accommodation may, therefore, be intrinsically linked to eye shape and resultantly AXL.

The true nature and causation of the dysfunction of the ciliary apparatus remain elusive. One proposal, based on longitudinal ocular growth data collected from emmetropic and myopic children, suggests that there is a developmental failure of ciliary body expansion which causes mechanical tension to be exerted by the crystalline lens or ciliary body (Berntsen *et al.*, 2012; Mutti *et al.*, 1998; Zadnik *et al.*, 1995). It is hypothesised that this tension inhibits equatorial globe expansion, resulting in elliptical expansion and therefore, axial elongation (Berntsen *et al.*, 2012). It follows that proportional growth and crystalline lens thinning could become insufficient to offset the axial elongation during emmetropisation leading to progressing myopia (Mutti *et al.*, 2012).

Berntsen *et al.* (2012) also suggest that an increased effort to accommodate may be required as a result of the higher ciliary/choroidal tension in myopes. This would result in higher lags of accommodation and AC/A ratios in these children. According to this theory, high accommodative lag in myopes would be a physiological effect of rather than a precipitant of myopia (Berntsen *et al.*, 2012). It is important to determine how any dysfunction of the ciliary apparatus may lead to ocular structural changes. Current opinion is that a deficit in the ciliary apparatus associated with accommodation inaccuracy is likely to produce central hyperopic retinal defocus, which could be a putative stimulant for axial growth by the same or similar mechanism to that described as a response to blur created with spectacle lenses (Berntsen *et al.*, 2012).

There is evidence to show that during accommodation there is a transient increase in AXL, which has been put forward as a potential trigger for myopia in those who do prolonged near work (Maheshwari *et al.*, 2011). This is supported by population studies in which it is demonstrated that groups that regularly perform high cognitive demand tasks have a much higher prevalence of myopia than those who do not (Goldschmidt, 1968; Simensen and Thorud, 1994).

Mallen *et al.* (2006) found that the transient increase in AXL is more marked in myopes. Axial elongation is 0.06 mm for myopes and 0.04 mm for emmetropes under conditions of 6.00 D of accommodation. This level of accommodation however far exceeds the task demand for near work in most normal situations. This suggests that this is unlikely to be the true mechanism stimulating axial growth. Woodman *et al.* (2011) have since shown that as myopia progresses a marked increase in transient AXL fluctuations occurs.

Accommodative inaccuracy may be a result of the inducement of accommodative lag at near, or via indirect means such as altered AC/A ratios, CA/C ratios or fusional reserves via an alteration in the synergistic link with the near vision triad. Studies have demonstrated a significant correlation between myopia progression and AC/A ratio as well as lag of accommodation (Gwiazda *et al.*, 2004; Mutti *et al.*, 2006; Price *et al.*, 2013).

Mutti *et al.* (2006) studied the accommodative lags of 1107 myopic (≤ -0.75 D) and emmetropic (-0.25 D to $+1.00$ D) children and concluded that though there were significant differences in accommodative lag for a 4.00 D target, this only became apparent after the onset of myopia and they concluded that it is, therefore, unlikely to be of value as a predictor for myopia development. Gwiazda *et al.* (1995; 1993) performed a longitudinal study of 80, six to 18 year old children including 26 who acquired myopia of at least -0.50 D and 54 who remained emmetropic (-0.25 D to $+0.75$ D). Non-cycloplegic refractive error, accommodation, and phorias were measured annually over a period of three years. It was found that myopic subjects accommodate less accurately than emmetropic subjects (Gwiazda *et al.* 1995; Gwiazda *et al.* 1993), this is supportive of the theory that hyperopic defocus may be a precipitant of human myopia (Mutti *et al.*, 2006). Increased response AC/As was also a feature of the myopic data; although these were not measured by Mutti. It was therefore concluded in contradiction to the prior

observations of Mutti *et al.* (2006) that oculomotor factors during near work tasks do seem to contribute to the genesis of myopia.

As a result of the above research Gwiazda and colleagues' COMET study (2004) and Berntsen *et al.*'s STAMP study (2012) were set up and both found statistically (not clinically) significant effects of the use of progressive addition lenses for slowing myopia progression. The children presenting with the greater degrees of accommodative lag and near esophoria were found to progress at the slowest rate after treatment with PALs in COMET. Although the positive addition increases accommodation accuracy by providing a relative myopic shift in the image shell, it is thought that the main factor altering progression rate may be an indirect modification of the inferior peripheral retinal image. Because of the near addition in PALs, a peripheral myopic shift in defocus in the superior retinal quadrant is expected compared with single vision lenses when a child is looking in primary gaze.

2. INSTRUMENTATION

2.1 Introduction

The technical specifications and operational procedures of instruments used for data collection in this thesis are described in this chapter. All instrumentation and ophthalmic drugs used within the project are standard instruments used in Optometric and/or Ophthalmological practice for the assessment of ocular function and health, although one instrument has a bespoke attachment commissioned for the collection of off-axis refractive data. This adaptation will also be discussed in detail. Details of experimental design specific to a single experiment are described in the relevant chapter.

2.2 Vision and visual acuity measurement

Distance monocular vision and visual acuity were recorded using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Precision Vision, La Salle, IL, USA) positioned at four metres from the participant. This instrument was used to determine if participants met eligibility criteria based on visual acuity in the studies described in Chapters 6 and 7.

LogMAR notation was used throughout the study. LogMAR charts address some of the widely recognised deficiencies of the Snellen chart and, therefore, allow for the most accurate quantification of vision and visual acuity (Ferris *et al.*, 1982). Perhaps most importantly for the scope of this study, it allows for consistent testing at all levels of visual acuity due to the equal number of optotypes per line and regular geometric progression in letter size (Bailey and Lovie, 1976).

The particular instrument used in this study is a portable device with an integrated light box to provide back illumination of the test card (see Figure 2.1). Though the chart is portable, it was positioned in the same location and position for all participants, thus allowing for more careful control and consistency of ambient lighting levels.

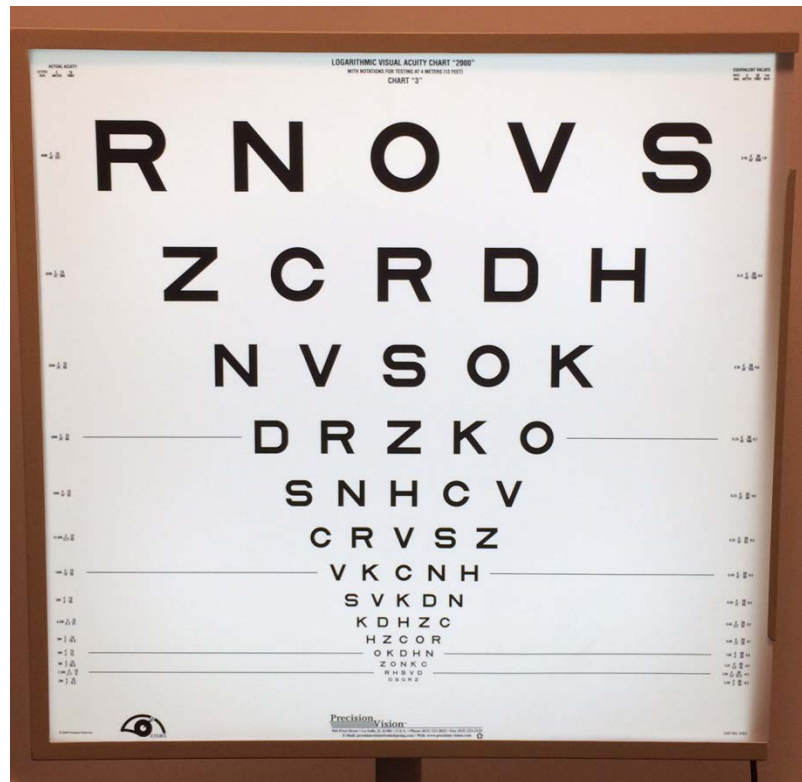


Figure 2.1 Illuminated 4m ETDRS chart.

2.3 Intra-ocular pressure

Assessment of Intra-ocular pressure (IOP) was made before cycloplegia for participants in the study described in Chapter 6, using the Tiolat iCare TA01 rebound tonometer (iCare Finland Oy, Finland). This instrument utilises the impact-rebound principle, whereby a magnetised probe is fired towards the cornea by a solenoid (Nakamura *et al.*, 2006). Motion data is analysed at the point where the probe makes contact with the cornea. Analysis of these motion parameters allows for the IOP at the time of impact to be calculated (Kageyama *et al.*, 2011). This instrument does not require topical corneal anaesthesia and has been shown to be better tolerated than non-contact techniques in

a child population (Kageyama *et al.*, 2011). Tonometry readings from the iCare tonometer have been found to be in reasonable agreement with Goldmann applanation tonometry (Abraham *et al.*, 2008; Van der Jagt and Jansonius, 2005), however other studies have reported an overestimation of IOP compared to Tonopen XL (Medtronic Solan, Jacksonville, FL) (Garcia - Resua *et al.*, 2006).

2.4 Cycloplegia

Cycloplegia was used prior to refractive data collection in the studies contained in Chapters 4, 5 and 6. Each eye was cyclopleged by the instillation of one drop of Cyclopentolate Hydrochloride 1% following instillation of one drop of Proxymetacaine Hydrochloride 0.5%. Both are supplied in minims (Bausch and Lomb UK Ltd). Cyclopentolate Hydrochloride is a muscarinic antagonist that is administered topically in optometric and ophthalmic practice to reduce ciliary muscle function, therefore, controlling accommodation.

Cyclopentolate acts as a blockade of the parasympathetic nervous system by preventing the miotic action of acetylcholine on the muscarinic receptors of the sphincter pupillae (Titcomb, 2003). Additionally, there is a blockade of ciliary muscle contraction (Siu *et al.*, 1999) preventing the crystalline lens from becoming more convex, resulting in impaired accommodative capability (Eperjesi and Jones, 2005). The binding of Cyclopentolate to muscarinic receptors is reversible, and the inhibitory effect is commensurate with the bioavailability of the drug (Siu *et al.*, 1999). It is important for practitioners to recognise that Cyclopentolate has a latent period of 30 - 40 minutes until cycloplegia is adequately established. Measurements taken during this period are likely to be unreliable unrepeatable and inaccurate (Eperjesi and Jones, 2005).

The use of topical anaesthesia before cycloplegia is common and is intended to increase absorption and drug effectivity to ensure that maximal cycloplegia is attained with the shortest latent period possible. Topical anaesthesia before cycloplegia has been found to shorten significantly the time taken to achieve maximum cycloplegia, especially in individuals with darkly pigmented irides (Siu *et al.*, 1999).

The pharmacological mode of action by which prior topical anaesthesia assists cycloplegia is not yet fully understood. It is unclear whether local anaesthetic has any interaction with Cyclopentolate at the receptor level (Siu *et al.*, 1999). It has been postulated that topical anaesthesia disrupts the corneal epithelium, leading to increased corneal permeability, enhancing the bioavailability and reducing the action time of Cyclopentolate (Herse and Siu., 1992). Using a topical anaesthetic and Cyclopentolate together may also prolong the presence of the drugs in the tears as reduced basal tear production and blink rate directly reduce the pre-corneal tear turnover rate (Patton and Robinson, 1975).

It is known that Cyclopentolate does not achieve absolute cycloplegia, with residual accommodation levelling at 1.50 D or less (Leat *et al.*, 1999). However, this is adequate for the scope of this study.

It has been reported that the presence of dilated pupils that are non-responsive to light along with a push-up amplitude of accommodation over 2.00 D is likely to reap unreliable and inaccurate measures of refraction (Amos, 2001). However, the presence of a small level of residual accommodation means that no adjustment of refraction needs to be made to account for ciliary muscle tonus (Viner, 2004). A Royal Air Force (RAF) Rule (Richmond Products, Albuquerque, NM) was used to check that the participants' accommodative amplitude had reduced to below two dioptres before proceeding to collect refraction data.

2.5 Biometry

Measures of AXL, anterior chamber depth (ACD) and corneal curvature (CR) were collected for all studies contained in this thesis (Chapters 4, 5, 6 and 7). Traditionally, A-scan ultrasound has been used to collect AXL and ACD data. However, A-scan has been largely superseded by the Zeiss IOLMaster (Carl Zeiss, Jena, GmbH) (see Figure 2.2). The IOLMaster is a non-contact technique that utilises the principle of partial coherence interferometry (PCI). Clinical advantages of the IOLMaster over A-scan include: negating the need for topical anaesthesia, avoiding the risk of corneal injury secondary to applanation, being less challenging for the patient and having greater precision.

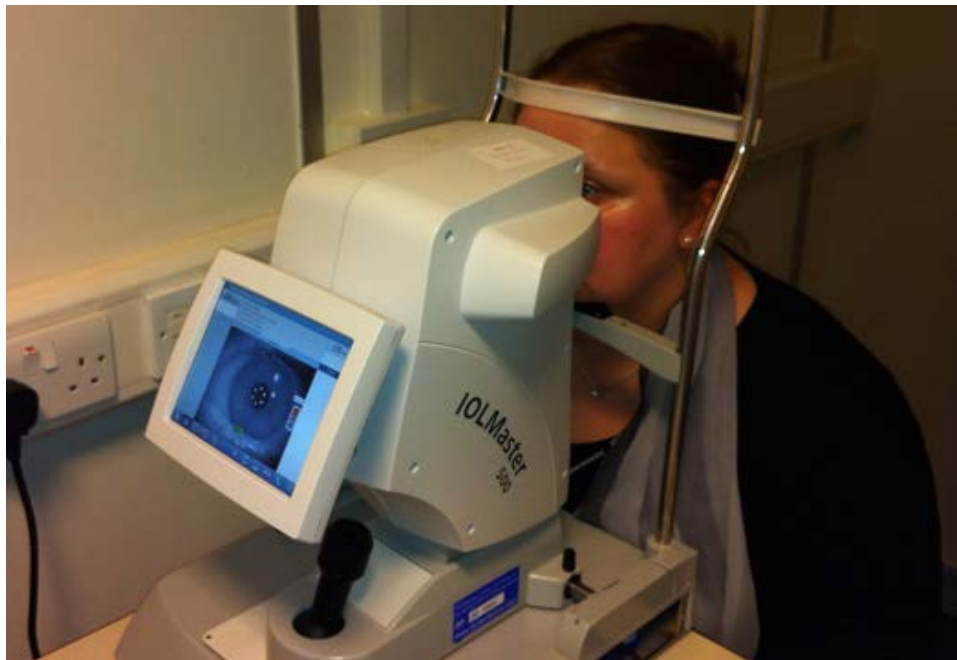


Figure 2.2 The Carl Zeiss IOLMaster 500.

2.5.1 Measurement of axial length

The IOLMaster has been widely reported as a safe, reliable and accurate instrument for AXL determination in adults (Goyal *et al.*, 2003; Kielhorn *et al.*, 2003; Lam *et al.*, 2001; Rose and Moshegov, 2003; Santodomingo-Rubido *et al.*, 2002) and children (Carkeet *et*

et al., 2004; Hussin *et al.*, 2006). The repeatability of optically measured AXL readings has been reported to be superior to those obtained by A - scan (Carkeet *et al.*, 2004; Hussin *et al.*, 2006; Kielhorn *et al.*, 2003). Data are, however, equivocal on whether there is an agreement between IOLMaster and A - scan data. Though Santodomingo-Rubido *et al.* (2002) and Hussin *et al.* (2006) both report almost perfect agreement between devices, other studies found IOLMaster readings to be consistently higher (Goyal *et al.*, 2003; Kielhorn *et al.*, 2003; Rose and Moshegov, 2003). Lam *et al.* (2001) reported that the IOLMaster produced slightly shorter AXL measurements than A - scan though this was not statistically significant.

Marginal discrepancies in ocular distance measurement may be attributable to ultrasound wavelengths being reflected from the internal limiting membrane, whereas PCI signals return from a deeper retinal structure: the RPE (Hussin *et al.*, 2006). Corneal indentation during ultrasound applanation also has the potential to result in shorter AXL values.

PCI uses an inbuilt infrared diode laser to measure the distance between the corneal apex and the retinal pigment epithelium (RPE) (see Figure 2.3). Light from the diode laser (λ 780 nm) is split into two equal coaxial beams (CB1 and CB2) by a beam splitter (BS1) which both then enter the eye. Reflections occur at the level of the cornea (CB1C and CB2C) and retina (CB1R and CB2R). The four light beams emerging from the eye enter a photodetector. The mirror (M1) is moved at a constant speed to produce a particular interference pattern. The resulting extent of the mirror displacement can be accurately measured and related to the signals received at the photoreceptor, for a precise quantification of corneal to retinal distance to be made (Santodomingo-Rubido *et al.*, 2008).



Figure 2.3 Operating principal of the IOLMaster. Reproduced with permission (Santodomingo-Rubido *et al.*, 2008) [A new non-contact optical device for ocular biometry, Santodomingo-Rubido, J., Mallen, E. A., Gilmartin, B. and Wolffsohn, J. S. British Journal of Ophthalmology Vol. 86, Copyright © 2002, BMJ Publishing Group Limited].

2.5.2 Measurement of corneal radius

The IOLMaster uses image analysis methods to measure the central corneal radius (Elbaz *et al.*, 2007). Measurements of corneal curvature taken by the IOLMaster closely correlate with those taken by conventional keratometers such as the Javal-Schiotz and videokeratoscopy (Németh *et al.*, 2003; Santodomingo-Rubido *et al.*, 2002).

To take a measurement, the practitioner aligns a graticule with a central light spot reflected from the participant's anterior tear film surface. Surrounding the central spot are six further points of light which are arranged in a hexagon of 2.3 mm diameter (Elbaz *et al.*, 2007). These light points must be brought into focus by manual manipulation of a joystick by the practitioner. Once adequately focussed, the joystick is depressed, on which the machine will take five rapid measurements of corneal radius, taking 0.5

seconds in total (Emerson and Tompkins, 2003). An average value for the curvature of each of the two principal meridians is displayed. The IOLMaster software derives these values by comparing the actual known separation of each of the three pairs of opposite light points with the imaged separation once projected onto the cornea.

2.5.3 Measurement of anterior chamber depth

Anterior chamber depth is measured along the optic axis, from the posterior face of the cornea to the anterior face of the crystalline lens. The IOLMaster projects a 0.7 mm wide optic section beam 38 degrees temporal to fixation through the anterior chamber (Emerson and Tompkins, 2003). The practitioner must align the corneal and lens sections within a boxed area marked on the instrument screen. On depression of the joystick, the instrument takes a photograph and measures the distance between the corneal vertex and the anterior lens section (Elbaz *et al.*, 2007; Santodomingo-Rubido *et al.*, 2002). An average of five readings is displayed.

The IOLMaster has been reported to give greater values for anterior chamber depth than with A-scan ultrasound (Elbaz *et al.*, 2007; Lam *et al.*, 2001; Santodomingo-Rubido *et al.*, 2002). It has been suggested that this may be due to compression of the globe during A-scan ultrasonography or due to the temporal positioning of the light source of the IOLMaster (Lam *et al.*, 2001).

2.6 Refractive error

Refractive error was measured objectively, using the Shin Nippon Nvision-K 5001 infrared autorefractor (Shin Nippon, Rexam, Japan) for all studies described in this thesis (Chapters 4, 5, 6 and 7). Autorefraction is appropriate for refractive error studies

as it is more repeatable than subjective refraction or retinoscopy (Bullimore *et al.*, 1998; Walline *et al.*, 1999; Zadnik *et al.*, 1992).

The Nvision-K 5001 is an open-view autorefractor, allowing the participant to view an object binocularly in free space. It is thought that this promotes the relaxation of accommodation, as well as reducing the influence of proximal accommodation (Tang *et al.*, 2014). The Nvision-K 5001 has been shown to be highly accurate and repeatable for on and off-axis measurement (Davies *et al.*, 2003), and has been used widely in studies of human refractive error (Chen *et al.*, 2010; Ehsaei *et al.*, 2011a; Ehsaei *et al.*, 2011b; Kang *et al.*, 2010; Logan *et al.*, 2005) and accommodation (Wolffsohn *et al.*, 2011; Yang *et al.*, 2011).

The Nvision-K 5001 can measure refraction and corneal curvature simultaneously (Nvision-K 5001 operations manual, 2004). Alignment of the participant and fixation can be monitored throughout the measurement session, on a colour LCD screen. The instrument first projects a ring target of infrared light through the entrance pupil of the eye that is then reflected by the retina. Following this, three infrared arcs of light of a smaller radius of curvature than the initial ring are projected. A motorised lens rack within the instrument brings the reflected images into focus, and the toroidal objective refraction is calculated by multiple-meridian digital analysis of the reflected image. Refractive prescriptions in the range of ± 22.00 D of spherical error and ± 10.00 D of cylindrical error in one-degree steps for cylinder axis can be measured (Davies *et al.*, 2003). The instrument can be programmed to measure at 0, 10, 12 and 13.5 mm back vertex distances. The machine also gives a value for interpupillary distance up to 85 mm.

2.6.1 Peripheral refraction

Recent years have seen increasing interest in the impact of peripheral refraction and its potential role in the failure of emmetropisation and subsequent ametropia, leading to the development of bespoke modifications to standard instruments to make them suitable for the collection of ocular shape data.

The Nvision-K 5001 has been cited as being both the most useful autorefractor and being valid for collecting measures of peripheral refraction (Fedtke *et al.*, 2009). This was mainly attributed to its ability to measure with a pupil aperture of 2.3 mm (Fedtke *et al.*, 2009).

For the study described in Chapter 6, a custom-made mechanical addition was fitted to the housing of the Nvision-K 5001 to allow for precise manipulation of fixation to obtain measurements at the desired eccentricities. This instrument is shown in Figure 2.4 and the mechanism for target-angle manipulation is shown in more detail in Figure 2.5. The instrument is mounted upon a wooden housing which sits over the casing of the autorefractor. A protractor and rotating disc attached to the peripheral arm allow it to be placed at differing eccentricities (Figure 2.5). The participant views a Maltese cross target through a Badal lens system also attached to the arm. The Badal Optometer (Badal, 1876) is an optical instrument which is used to present a target of constant angular size at a range of vergences to the eye (Smith and Atchison, 1997). The Badal system was set up using a + 5.00 D lens at a distance of 20 cm to induce zero accommodation (see Figure 2.4).

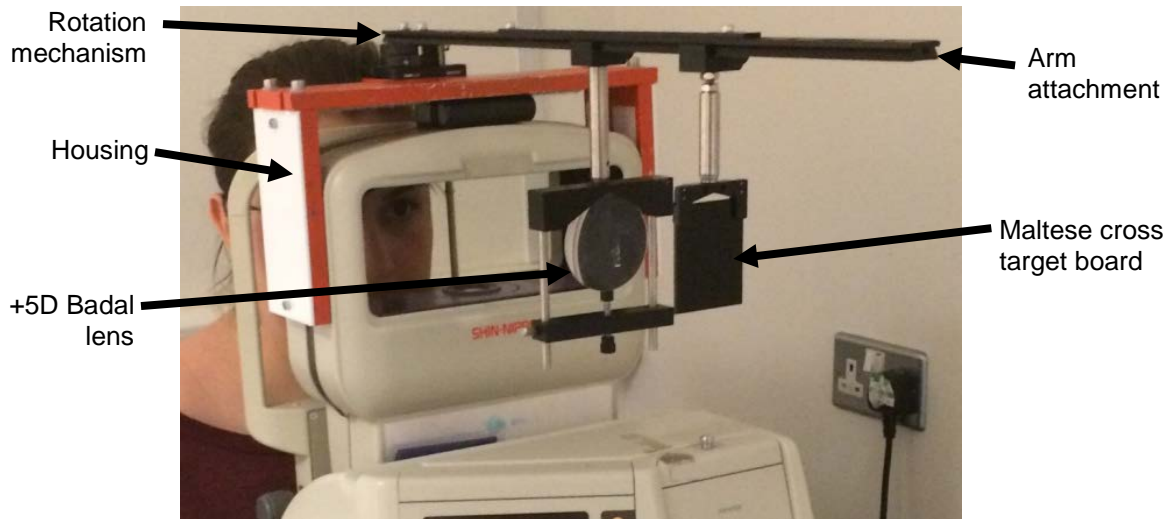


Figure 2.4 Shin Nippon NVision-K 5001 with a custom attachment for peripheral refraction.

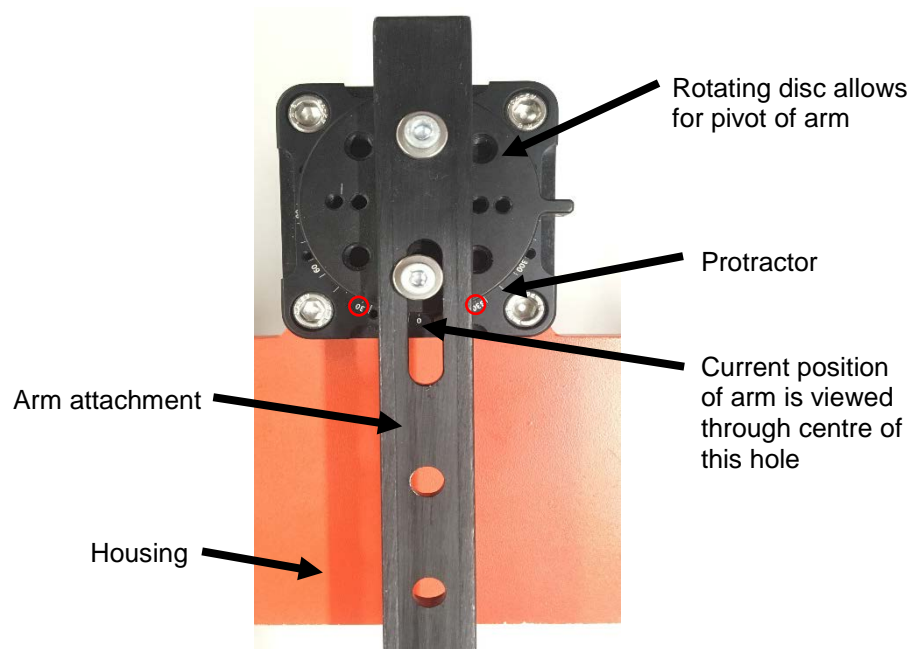


Figure 2.5 Aerial view of the mechanism which allows for rotation and alignment of the peripheral refraction instrument. Alignment positions 30 degrees from fixation are circled in red.

The eye which was not being measured was occluded with an eye patch. The measured points were at ten-degree increments to a maximum eccentricity of 30 degrees nasal and temporal to the fovea along the horizontal meridian. The casing for the auto refractor would likely occlude visualisation of the fixation target at angles any more eccentric than this. An average of three readings at each location was taken. The order that the positions are measured in was determined by the random selection of cards that were shuffled between visits.

2.7 Perimetry

Perimetry is a key parameter in the assessment and monitoring of visual function in patients with ophthalmic and neurological diseases (Harbert *et al.*, 2012). In children, the feasibility and reliability of formal perimetric assessment improves with age (Patel *et al.*, 2015). Clinical visual field assessment is achievable in children from the age of five years (Patel *et al.*, 2015). HFA SITA algorithms and Goldmann perimetry are the two most common perimetric approaches in children with suspected or confirmed visual field loss in UK hospitals (Walters *et al.*, 2012).

The studies presented in this thesis examine a wide age range of child participants, from five to 15 years of age. Different tests were used depending on the study, participant's age, ability and level of cooperation.

For the study presented in Chapter 6, Goldmann Bowl perimetry was performed on participants with retinal pathology (see Section 6.3 for further information). The extent of the visual field was assessed monocularly using standard clinical methodology as used in ophthalmological practice (V4e kinetic target). The Goldmann perimeter has been shown to be the measure of choice for changes in peripheral vision and test-retest variability can be < 20% (Bittner *et al.*, 2011). The target was brought from non-seeing

to seeing along a minimum of six meridians, including the superior, inferior nasal and temporal directions. The tested points were mapped and connected with straight lines to form isopters.

Visual fields were measured using the Carl Zeiss Humphrey Field Analyser 750 (HFA) for the study presented in Chapter 7 (specific details of testing algorithms and methods will be presented in detail in Section 7.2). The HFA is considered to be the gold standard automated perimeter. The test requires the participant to fixate on a central light target within a bowl-shaped screen while responding to the presentation of discrete peripheral light stimuli.

Small amounts of defocus due to sub-optimal or lack of refractive correction are capable of causing a reduction in retinal sensitivity during perimetry (Weinreb and Perlman, 1986). Therefore, it is imperative that optimal refractive correction must be worn to correct both spherical and astigmatic errors during visual field testing. Clear contact lenses or full aperture trial case lenses are suitable modalities of correction for perimetry. The use of full aperture lenses negates the problem of artefacts often caused by the frames of reduced aperture or spectacle lenses.

2.8 Fundus photography

Photographs of both fundi were taken for children participating in the study described in Chapter 6, using the Topcon TRC - NW8 non-mydratic fundus camera (Topcon Corporation, Tokyo, Japan) (see Figure 2.6). This model has nine internal fixation points, which facilitate the composition of wide-angle views of the retina, which is of particular advantage when imaging peripheral retinal pathology.



Figure 2.6 The Topcon TRC - NW8 fundus camera.

2.9 Data analysis and statistics

Raw data were inputted into a Microsoft Excel spreadsheet (Microsoft Corporation, Washington, USA). All statistical analyses were carried out using SPSS version 21 (SPSS Incorporated, Chicago). Both parametric and non-parametric tests were used, depending on the distribution of the data. These tests will be described in further detail in the experimental chapters of this thesis.

3. INTRODUCTION TO STUDY OBJECTIVES

This thesis has been written to describe a collection of studies encouraged by the increasing prevalence and epidemic of myopia, with the primary aim of producing a cohesive investigation of the impact of central and peripheral retinal disease on myopia progression. The initial protocol and background to this study as approved by the *National Research Ethics Service* is presented in Appendix 10.8. However, recruitment to this study was severely limited and resultantly, the original study objectives were not met. This complication necessitated a departure from the study's original design and aims. Though the proposed research question could not be answered and the scope of the study is much curtailed, data collected for the original project is still utilised, taking the form of a feasibility study (Chapter 6). Instead, data from previous studies is analysed alongside newly collected data, to produce a collection of unique studies on the biometry of myopic and non-myopic eyes more broadly.

To benefit the overall flow of the thesis, the studies and their data have not been ordered chronologically with regards to when the data were collected / analysed, but rather in an order which allows for the presentation of studies producing normative data prior to the later studies which draw comparisons with them. For further clarity and to assist the reader, an explanation of the order and content of the experimental Chapters of thesis as set-out within is detailed below.

Chapter 4 describes a large sample, cross-sectional, study in which *Decision Tree Analysis* is used to investigate the influences of: axial length, refractive group, age, ethnicity and gender on the well-known axial length: refractive error ratio. Research questions are: (a) does axial length, refractive group, age, ethnicity or gender influence variations in this ratio in healthy eyes? (b) Is any relationship between axial length and this ratio predicted by effectivity? (c) What are the normative variations?

Chapter 5 contains a description of another large sample, cross-sectional, study in which *Decision Tree Analysis* is used to investigate the influences of: axial length, refractive group, age, ethnicity and gender on corneal and refractive astigmatism (power and axis orientation). Research questions are: (a) Does axial length, refractive group, age, ethnicity or gender influence these forms of astigmatism in healthy eyes? (b) What are the normative variations?

Chapter 6 presents a feasibility study on the investigation of peripheral refraction and axial length in eyes with peripheral retinal disease. This is an appended version of the project initially designed. Research questions are now: (a) Is studying eyes with these forms of ocular disease feasible? (b) At first glance, do the cases show striking differences to the normative data provided by Chapters 4 and 5?

Chapter 7 contains a feasibility study on the influence of axial length and refractive error on central and peripheral retinal light sensitivity. Research questions are: (a) Does retinal light sensitivity depend on axial length and refractive error? (b) Can this tell us anything about the nature of retinal stretching in myopia?

The final chapter (Chapter 8) provides a summary of the research, reviews the answers to the research questions, comments on study limitations and makes recommendations for further research.

4. THE INFLUENCE OF AGE, REFRACTIVE GROUP, ETHNICITY AND GENDER ON THE RELATIONSHIP BETWEEN AXIAL LENGTH AND REFRACTIVE ERROR

4.1 Background

A strong negative correlation between AXL and refractive error has been shown in both adult (Bullimore *et al.*, 1992; Chui *et al.*, 2008; Grosvenor and Scott, 1993; Strang *et al.*, 1998) and child populations (Gwiazda *et al.*, 2002; Lam *et al.*, 1991). It is also clear that changes in eye size or its components are responsible for changes in the refractive properties of the eye (Gwiazda *et al.*, 2002). It is well established that axial elongation is the main correlate responsible for myopia progression during childhood (Grosvenor and Scott, 1991; Grosvenor and Scott, 1993; Larsen, 1971; Mutti *et al.*, 2012; Sorsby *et al.*, 1961; Sorsby and Leary, 1970; Stenstrom, 1948). Studies have shown that while after the first few years of life corneal power does not alter significantly; there is a gradual reduction in lens power with age (Mutti *et al.*, 2005; Zadnik *et al.*, 1995; Zadnik *et al.*, 2003). However, a consistent course of AXL change with age has not yet been identified (Atchison *et al.*, 2008; Grosvenor, 1987b; Koretz *et al.* 1989; Leighton and Tomlinson, 1972; Ooi and Grosvenor, 1995). It, therefore, seems likely that the correlation between AXL and refractive error may alter at different stages of ocular development as the compensatory relationship between the lens and the AXL changes.

As discussed in Section 1.3.2, axially myopic eyes have longer AXLs than eyes that are emmetropic or hyperopic (Mayer *et al.*, 2001; Mutti *et al.*, 2005). Studies by Atchison *et al.* (2004) and Deller *et al.*, (1947) found that the mean increase in AXL per dioptre of myopia was 0.33 mm and 0.35 mm respectively for an adult population. It is known that the relationship between ocular components is not stable throughout emmetropisation, and so it follows that there may be potential for the relationship between refractive error

and axial length to vary according to age, and, therefore, these values may not be applicable to children.

Calculations based on the manipulation of Gullstrand reduced model eye parameters (power 60 D; refractive index, 1.33; radius; 5.5 mm; AXL, 22.5 mm) predict a reduction in MSE: AXL ratio as the axial length of the eye is increased. In this modelling, AXL is adjusted to produce refractive errors ranging from hyperopia to myopia. Refractive error is then plotted as a function of AXL. A line of best fit plotted through the data demonstrates the non - linearity and non - constant nature of the relationship (see Figure 4.1).

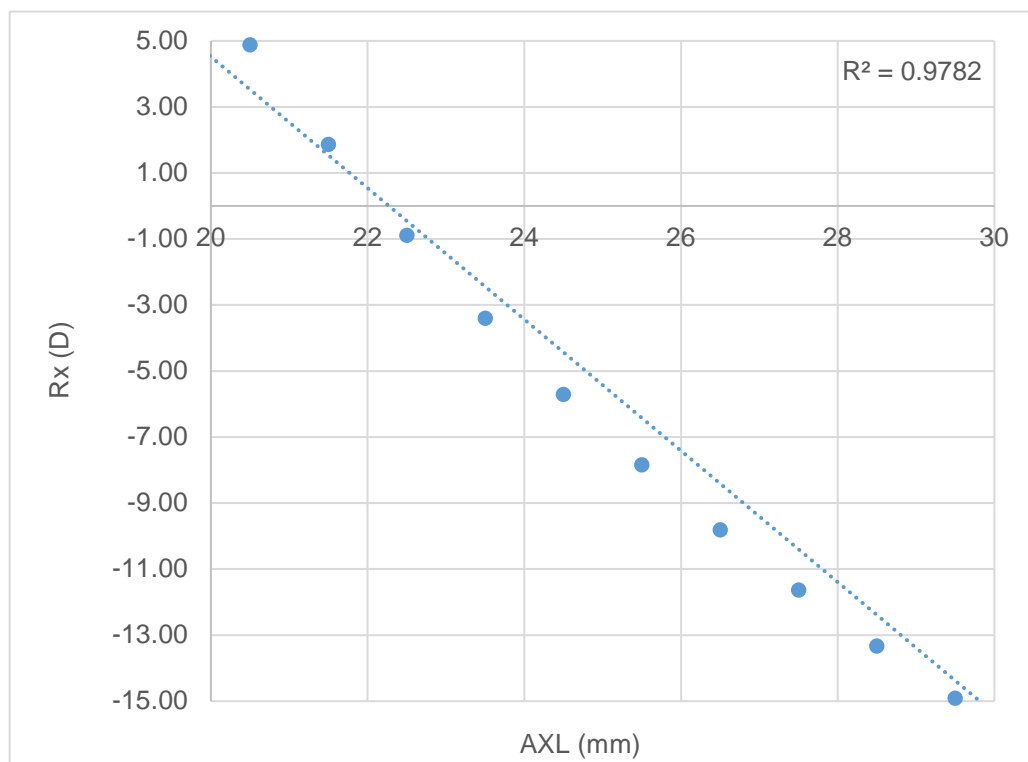


Figure 4.1 The relationship between axial length (AXL) and refractive error (Rx) as predicted from calculations using Gullstrand reduced model eye parameters.

The predicted magnitude of the reduction in the dioptre per mm of AXL expansion relationship is shown in Table 4.1. Determining the relationship between AXL and refractive error is an essential consideration in studies investigating the effects of myopia control, particularly when assessing the efficacy of myopia control interventions based

on axial length changes as the principal outcome measure and when considering target treatment age. As the main aim of myopia control interventions is to limit axial expansion, it is important to be able to gauge efficacy as a one millimetre difference may correspond to differing amounts of ametropia in differently aged populations.

AXL (mm)	AXL (m)	L (D)	L' (D)	Rx (D)	D/mm of change
19.5	0.0195	-68.21	-8.21	8.21	-
20.5	0.0205	-64.88	-4.88	4.88	3.33
21.5	0.0215	-61.86	-1.86	1.86	3.02
22.5	0.0225	-59.11	0.89	-0.89	2.75
23.5	0.0235	-56.60	3.40	-3.40	2.52
24.5	0.0245	-54.29	5.71	-5.71	2.31
25.5	0.0255	-52.16	7.84	-7.84	2.13
26.5	0.0265	-50.19	9.81	-9.81	1.97
27.5	0.0275	-48.36	11.64	-11.64	1.83
28.5	0.0285	-46.67	13.33	-13.33	1.70
29.5	0.0295	-45.08	14.92	-14.92	1.58
30.5	0.0305	-43.61	16.39	-16.39	1.48
31.5	0.0315	-42.22	17.78	-17.78	1.38
32.5	0.0325	-40.92	19.08	-19.08	1.30
33.5	0.0335	-39.70	20.30	-20.30	1.22

Table 4.1 Output values of Gullstrand reduced model eye calculations demonstrating that optical theory predicts a reduction in the Rx: AXL ratio as AXL increases (see D/mm of change column).

A recent systematic review and quantitative meta-analysis of the worldwide prevalence of myopia in childhood and adolescence by Rudnicka and colleagues (2016) quantified the striking ethnic differences in myopia prevalence, which become more marked with age. These differing prevalences are detailed in Table 4.2. East Asians showed the highest prevalence of myopia (≤ -0.50 DS) and highest increase in prevalence over time, with over 90% of Singaporean East Asians and 72% of Chinese East Asians aged 18 years exhibiting myopia (Rudnicka *et al.*, 2016). South Asians however, had much lower rates with limited evidence of change over time. Interestingly, there were marked differences between those living in South Asia compared with migrant South Asian

populations (Rudnicka *et al.*, 2016). As myopia prevalence figures alter dramatically according to geographic location it also seems crucial to determine whether the relationship between refractive error and AXL is influenced by ethnicity at different stages of ocular development.



Table 4.2 Estimated prevalence of myopia by age and ethnicity in boys and girls combined. Reproduced with permission (Rudnicka *et al.*, 2016) [Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention, Rudnicka, A. R., Kapetanakis, V. V., Wathern, A. K., Logan, N. S., Gilmartin, B., Whincup, P. H., Cook, D. G. and Owen, C. G. British Journal of Ophthalmology, Vol 100, Copyright © 2016 BMJ publishing Group Limited].

This study will first determine normative data for AXL and refractive error correlations, and then examine if they are influenced by age, gender and ethnicity in a cross-sectional sample of two groups of UK children (aged six to seven and 12 - 13 years) and one group of UK adults (aged 18 - 25 years). The skew and kurtosis of refraction and ocular biometric parameters will also be assessed. This study examines children and young adults from the Birmingham area of the UK, which has high ethnic diversity. Comparisons will be made with similar UK and non-UK studies, which are on largely ethnically homogenous white populations. Pre-presbyopes were chosen as lens changes in incipient presbyopia or presbyopia itself may influence and alter a subject's refraction. This study will then determine the association between the amount of myopia per

millimetre of axial expansion in the different age groups. The influences of gender and ethnicity on the Rx: AXL ratio will also be examined.

4.2 Methods

4.2.1 Participants

This chapter presents an analysis of data previously collected by Dr Parth Shah and colleagues for the 'Aston Eye Study' (AES) a cross-sectional study designed to determine the prevalence and associated ocular biometry of refractive error in a large multi-racial sample of school children from the metropolitan area of Birmingham, UK. Data are also analysed for a cohort of adult participants which were collected on a student population by Dr Nicola Logan and colleagues at Aston University, Birmingham, UK.

AXL and refractive error data were analysed for 760 subjects (365 male, 395 female) across three cohorts. Data for two separate cohorts of children, who participated in the AES were analysed as well as data for one cohort of 18 - 25 year olds recruited from Aston University's Optometry student body. To aid comparison with previous studies of childhood refractive error and astigmatism, the AES recruited children either aged six - seven or 12 - 13 years of age (Ojaimi *et al.*, 2005; O'Donoghue *et al.*, 2010).

The AES is a cross-sectional study of childhood refractive error conducted in Birmingham, England. A stratified random cluster sampling strategy was used for recruitment for this study. This system was devised based on known information about schools in the relevant geographical area (Logan *et al.*, 2011). Target schools for the AES were stratified taking age and deprivation index of the geographical ward into consideration. Birmingham is made up of 40 separate 'wards'. Each of these wards is

given an *index of multiple deprivation* score, which is reflective of the wards individual deprivation characteristics (<http://www.birminghameconomy.org.uk>). Tertiles of deprivation were created using data from January 2000 (<http://www.statistics.gov.uk>), and these were used to stratify the sample. This technique was used to ensure an equal representation of schools from each deprivation category.

2004 census data (National Statistics Office, <http://www.statistics.gov.uk>) was used to determine the ethnic composition of children resident in Birmingham. The criterion of the sampling models were picked in order to recruit schools with a sufficient ethnic mix, and to include children from similar ethnic backgrounds with similar demographic and educational characteristics (Logan *et al.*, 2011). The ethnic composition of each school was incorporated into the sampling models, using information provided by Birmingham City Council (Logan *et al.*, 2011). Schools with a proportion of children of any one ethnicity $\geq 70\%$ were excluded from the study.

4.2.2 Instrumentation

Refractive error was measured with an open-field autorefractor (Shin Nippon, Rexam, Japan) while AXL was assessed with an IOLMaster 500 (Carl Zeiss, Jena, GmbH). One drop each of Proxymetacaine Hydrochloride (0.5%) and Cyclopentolate Hydrochloride (1%) (Minims, Chauvin Pharmaceuticals) were administered to child participants before measurement. Participants were instructed to focus on a maltese cross target placed at a distance of four metres. The average was taken from a minimum of five reliable readings for both refractive and AXL data. See Chapter 2 for more information on these devices.

4.2.3 Group demographics

Measurements were taken on the right eyes of three age-specific cohorts of participants; Children participating in the AES aged six to seven years inclusive (n = 343): Children participating in the AES aged 12 to 13 years inclusive (n = 294) and adult participants (age 18 to 25 years inclusive, n = 123) recruited from Aston University's Optometry student body.

The majority of subjects averaged across age groups were of British South Asian (56.3%) or white ethnicity (24.7%). See Table 4.3 for a breakdown of cohort demographics by age group.

	Number	Age (years)		Ethnicity (%)		Gender (%)	
6-7 years	343	Mean	7.1	South Asian	61.2	Female	Male
		SD	0.35	White	19.2		
		Range	6.1 to 7.9	Black	12.5		
12-13 years	294	Mean	13.1	Mixed	4.4	48.1	51.9
		SD	0.32	Other	1.8		
		Range	12.3 to 13.9	East Asian	0.9		
18-25 years	123	Mean	20.6	South Asian	85.4	Female	Male
		SD	1.91	White	7.3		
		Range	18.1 to 25.8	Black	2.4		
				Mixed	1.6	54.5	45.5
				Other	2.4		
				East Asian	0.8		

Table 4.3 Cohort demographics by age group.

4.2.4 Ethical considerations

Ethical approval was granted by Aston University Research Ethics Committee. The research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from adult participants and each child's parent or guardian before participation in the study.

4.2.5 Sample size calculation

A priori power analysis was performed using G*Power 3 (Faul *et al.*, 2007). A two-tailed, linear bivariate regression (one group, size of slope) with an α level of 0.05 and a β level of 0.2 was performed to compute required sample size. Calculating for a medium effect size of 0.3 (Cohen, 1988; Prajapati *et al.*, 2010) resulted in a total required sample size of 82 in each group. Division by the asymptotic relative effectivity correction (ARE 0.91) for non-parametric data adjusted the sample size to a total requirement of 91 participants per group.

4.2.6 Statistical analysis

Distributions of refraction and AXL are described in terms of central tendency and spread (mean and SD), skewness and kurtosis. Statistical analysis of skewness and kurtosis enables further characterisation of the location and variability of the data. Skewness is a measure of the lack of symmetry of a data set around its centre point. Kurtosis is a measure of the number of outliers relative to a normal distribution. Data sets with low kurtosis tend to have 'heavy tails' (outliers), while sets with low kurtosis have light tails (a lack of outliers) (Laerd statistics ©, 2013, Lund Research Ltd.).

Results of correlation gradients, Mann - Whitney U testing, Spearman's rank - order correlation and Decision Tree Analysis (DTA) are all reported. All confidence intervals

(CI) are 95%. For this study, myopia was defined as MSE refraction (sphere + (cylinder / 2)) ≤ -0.50 D, emmetropia as MSE > -0.50 D to $< +2.00$ D, and hyperopia as MSE $\geq +2.00$ D.

Decision tree analysis (DTA) using the chi-squared automatic interaction detection (CHAID) method was also performed to determine the hierarchical influence of each nominal independent variable on the dependent variables. DTA is a form of multivariate analysis where each node of a decision tree represents a statistical analysis on an attribute, while the branches represent the outcomes of the individual tests. The advantage of this form of analysis is that all variables are accounted for at once, therefore influence of confounding is removed. DTA and CHAID have previously been used by other studies in the field of optometry to achieve multivariate analysis (Dunstone *et al.*, 2013; Guillon and Maissa, 2005).

At each stage of the analysis, chi-squared testing was performed at splitting and Bonferroni adjustments were applied to p-values to account for multiple testing. At each stage, the strongest interaction with the dependant variable is determined by CHAID. The CHAID model contains a series of nodes, including the the root node (the dependant variable), parent nodes (a node which has other nodes stemming from it) and child nodes (a node coming from another node). It has been suggested that minimum node sizes should be set depending on overall sample size (Collins *et al.*, 2010) and for larger sample sizes a minimum size of 20 for the parent node and 10 for the child node is appropriate (the Measurement group 1999-2005). For the purposes of this study, parent nodes of 30 and child nodes of 15 were used, as a sample size of 30 is generally accepted as large enough to define as a population and is therefore large enough to analyse (Bailey, 2008).

4.3 Results

4.3.1 Prevalence of myopia

The prevalence of myopia (MSE = ≤ -0.50 D) was 8.8% (CI, 5.8 – 11.7) in the six - seven years cohort, 26.5% (CI, 21.5 – 31.6) in the 12 - 13 year-old cohort and 54.5% (CI, 45.7 – 63.3) for the 18 - 25 years group.

4.3.2 Normality of data

Normality of the data was tested using a Shapiro-Wilk test. For all groups, the mean spherical refractive error was not normally distributed ($p < 0.05$). AXL was normally distributed in all groups. p values were as follows: children aged six - seven, $p = 0.15$, 12 to 13 years $p = 0.56$ and adult group $p = 0.61$. See Table 4.4 for mean MSE and AXL values for each cohort. Analyses of skewness and kurtosis are presented in Table 4.5.

Age Group	Mean MSE (D)	SD	Range (D)	Mean AXL (mm)	SD	Range (mm)
6-7	+0.87	1.39	+7.60 to -8.81	22.70	0.78	19.66 to 25.26
12-13	-0.06	1.42	+5.56 to -5.66	23.49	0.86	20.56 to 26.09
18- 25	-1.41	1.95	+3.08 to -10.48	23.98	1.12	21.40 to 27.70

Table 4.4 Mean MSE and AXL values for each cohort.

		6 – 7 years			12 – 13 years			18 – 25 years		
			SE	Z		SE	Z		SE	Z
MSE	Skew.	-0.90	0.13	-6.83	-0.62	0.14	-7.04	-1.42	0.22	0.65
	Kurt.	13.55	0.26	51.50	3.63	0.28	12.83	3.05	0.43	7.04
AXL	Skew.	-0.12	0.13	-0.87	-0.09	0.14	-0.64	0.28	0.22	1.29
	Kurt.	0.85	0.26	3.24	-0.34	0.28	-1.22	0.33	0.43	0.77

Table 4.5 Skewness, kurtosis and z values for each cohort. AXL and MSE are presented separately. For both skewness and kurtosis, z-scores within ± 2.58 are determined to be normally distributed (Laerd statistics ©, 2013, Lund Research Ltd).

4.3.3 Correlation between MSE and AXL

A Spearman's rank - order correlation was run to assess the relationship between MSE and AXL for all three of the participant groups. Preliminary analysis showed the relationship in each group to be monotonic, as assessed by visual inspection of a scatterplot. There was a significant negative correlation between MSE and AXL in all three groups. The results were as follows; children aged six - seven, $r_s(341) = -0.37$ $p = < 0.005$ (see Figure 4.2), children aged 12 - 13, $r_s(292) = -0.48$, $p = < 0.005$ (see Figure 4.3) and adults, $r_s(121) = -0.68$, $p = < 0.005$ (see Figure 4.4).

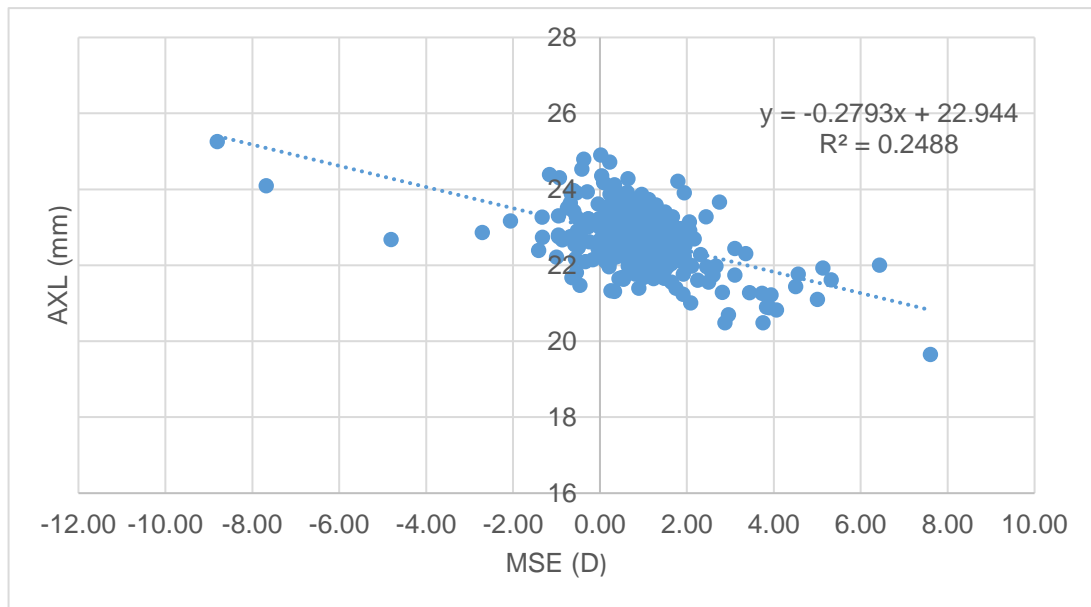


Figure 4.2 The correlation between AXL (mm) and MSE (D) for children aged six - seven years.

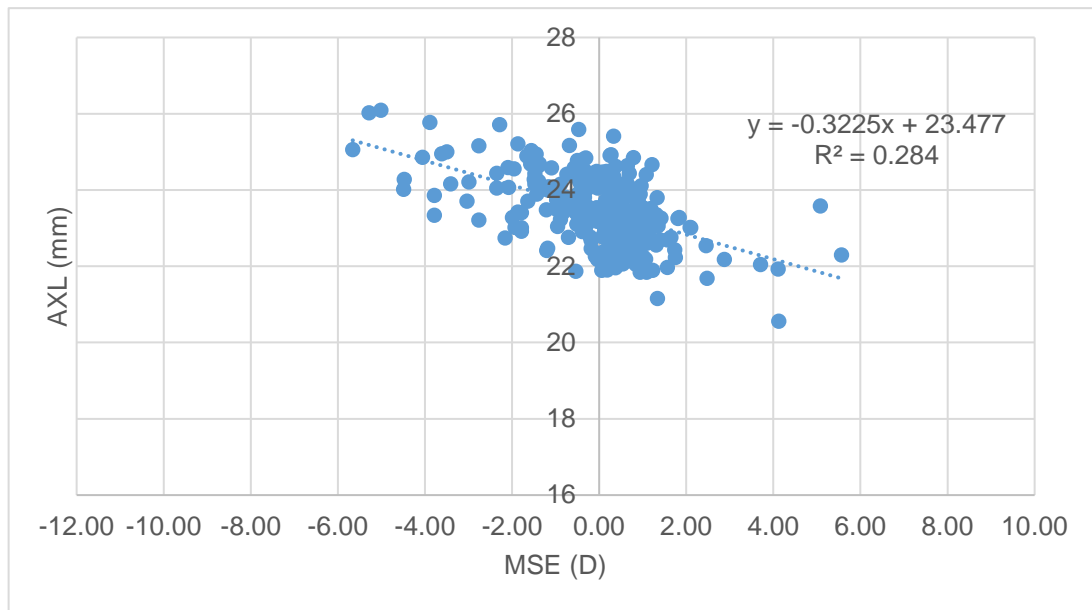


Figure 4.3 The correlation between AXL (mm) and MSE (D) for children aged 12 - 13 years.

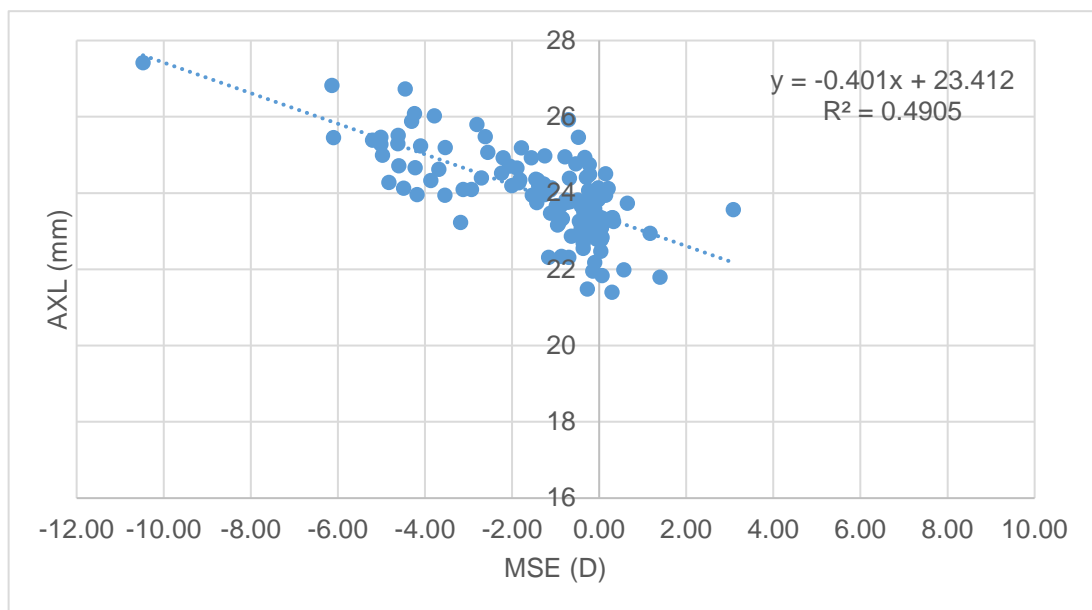


Figure 4.4 The correlation between AXL (mm) and MSE (D) for adults aged 18 - 25 years.

4.3.4 Refractive change per unit of axial expansion

Theoretical dioptric values per 1 mm increase in AXL were derived by calculating the inverse of the regression slopes. For the specific cohorts, 1 mm increase in AXL would

correlate with - 3.58 D of refractive change for the six - seven year olds, - 3.10 D for the 12 – 13 year olds and - 2.49 D for the young adult group. To enable comparison with previous studies, this equates to values per dioptre of increasing myopia as 0.28 mm for the six - seven year olds, 0.32 mm for the 12 – 13 year olds and 0.40 mm for the 18 – 25 year olds.

4.3.5 Distribution of data by gender

Table 4.6 shows the distribution of mean AXL measures by age group and gender, while Table 4.7 shows the distribution of mean MSE by gender.

Group	Female			Male			MWU
	Mean (mm)	SD	Range (mm)	Mean (mm)	SD	Range (mm)	<i>p</i> value
6-7	22.49	0.76	20.49 to 25.26	22.90	0.75	19.66 to 24.91	<0.005
12-13	23.32	0.88	20.56 to 26.09	23.71	0.79	21.90 to 25.71	<0.005
18-25	23.99	1.22	21.40 to 27.42	23.96	0.98	21.49 to 26.83	0.93

Table 4.6 Distribution of AXL by age group and gender. *p* values from Mann - Whitney U (MWU) statistical analysis of the difference in distribution between female and male participants are presented in the rightmost column.

Group	Female			Male			MWU
	Mean (D)	SD	Range (D)	Mean (D)	SD	Range (D)	<i>p</i> value
6-7	0.83	1.64	6.43 to -8.81	0.91	1.11	7.60 to -2.06	0.98
12-13	-0.26	1.56	4.12 to -5.66	0.132	1.22	5.56 to -3.61	0.28
18-25	-1.87	2.20	1.39 to -10.47	-0.85	1.42	3.08 to -6.14	0.01

Table 4.7 Distribution of MSE by age group and gender. *p* values from MWU statistical analysis of the difference in distribution between female and male participants are presented in the rightmost column.

Results of Mann - Whitney U analysis showed that there was a significant difference in the distribution of AXL between males and females in both the six - seven and 12 - 13 year age groups ($p = < 0.005$) and that female participants had a significantly shorter

AXL than males (six – seven years = 22.49 mm vs. 22.90 mm and 12 - 13 years = 23.32 mm vs. 23.71 mm). However, no significant difference was found in the distributions for the 18 to 25 years age group ($p = 0.93$).

Conversely, in terms of MSE, Mann - Whitney U testing found that there was no significant difference in the distribution of MSE between male and female participants for the six -seven and 12 - 13 years age groups ($p = 0.98$ and $p = 0.28$ respectively). Females in the adult group were found to have significantly more myopic mean spherical errors than male subjects (- 1.87 D vs. - 0.85 D, $p = 0.01$).

4.3.6 Factors influencing Rx: AXL ratio - decision tree analysis

Decision tree analysis (DTA) was performed with Rx: AXL ratio as the dependent variable, and independent variables of: age, gender, ethnicity, refractive grouping and axial length. The output of this analysis is shown in Figure 4.5.

For the purposes of this analysis, Rx: AXL ratio was determined for each participant by dividing MSE refractive error (D) by axial length (mm). To aid clarity and interpretation, each ratio was then classified as either > 3 mm/D or < 3 mm/D. The independent variables age group, gender and ethnicity were all analysed directly, whereas axial length was categorised as 'below average', 'average' or 'above average' based on the average axial length value for participants in their corresponding age cohort.

No association was found between Rx: AXL ratio and ethnicity, gender or axial length (all $p > 0.05$). The first nodal splitting occurred on the basis of refractive error category (myopic, emmetropic or hyperopic), with 82.2% of emmetropes having a Rx: AXL ratio of less than 3 mm/D, compared to 61.1% of myopic or hyperopic participants ($X^2 (1) = 38$, $p = < 0.005$). The myopic/hyperopic node then differentiated further on the basis of

age with adult participants more likely to have ratios less than 3 mm/D than child participants (adult ratio < 3 mm/D = 76.5% vs. child ratio < 3 mm/D = 54.2%, $X^2(1) = 9$, $p = 0.005$). The final child node of the DTA was a subsequent splitting of the child participants resulting in a differentiation between myopes and hyperopes, with myopes less likely to have a ratio of < 3 mm/D compared to hyperopes (myopes 49.1 % vs. hyperopes 66.7%, $X^2(1) = 3$, $p = 0.05$).

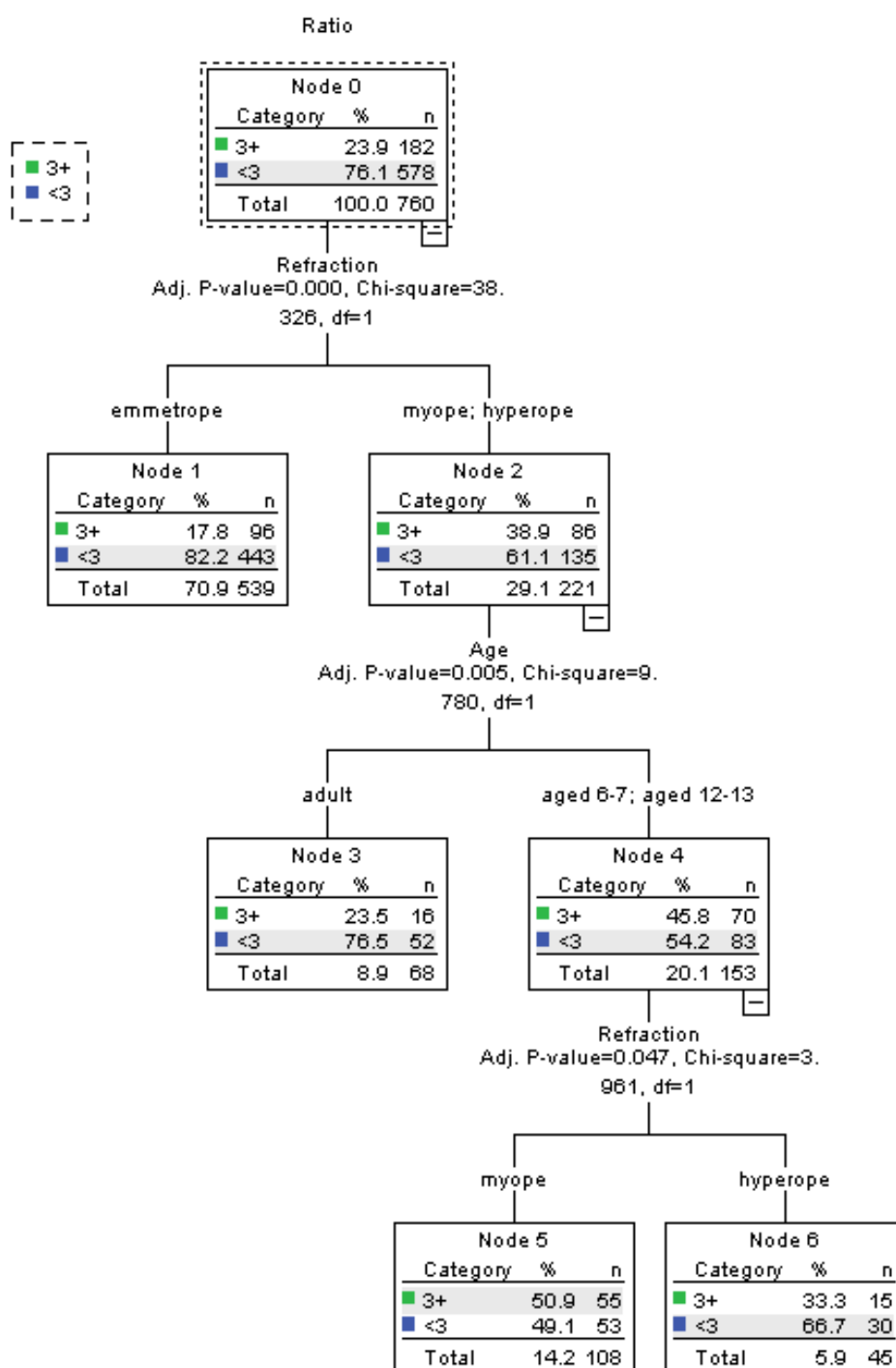


Figure 4.5 Decision tree output of the influence of the dependent variables age, gender, ethnicity, refractive grouping (refraction) and axial length on the Rx: AXL ratio.

4.4 Discussion

As this is a cross-sectional study, the conclusions drawn from this data are not applicable to specific changes within individual eyes over time, rather, they apply to populations in general. However, these findings provide a cross-sectional measure of a large group of ethnically diverse UK children and adults with a wide range of refractive errors.

There was a myopic shift in mean MSE between younger and older cohorts (see Table 4.4). The prevalence of myopia in this study was 8.8% for the six to seven year olds, 26.5% for the 12 - 13 year olds and 54.5% for the adult group. For both child cohorts, the prevalence of myopia is considerably higher than that found in either the SMS or NICER studies (6-7 years prevalence NICER = 2.0%, SMS = 0.7%, 12-13 years prevalence NICER = 15%, SMS = 4.6%) (French *et al.*, 2012). The finding in the 12 - 13 year olds is more comparable with the USA CLEERE study which found a prevalence of 23.8% (Mutti, D., oral communication, September 2011, as cited in French *et al.*, 2012). The prevalence of myopia in adults in this study, though higher than expected in a general population, is consistent with previous cross-sectional studies of student populations, such as the work of Logan *et al.* (2005) who found a myopia prevalence of 52.7% in a sample of 373 Aston University, UK students (mean age 19.55 years, SD = 2.99). It is also comparable to the Scandinavian studies of Fledelius *et al.*, 2000 and Kinge *et al.*, 1998, who found prevalences of 50% and 47% respectively. The finding of this study is however slightly lower than that of Loman *et al.*, 2002 who found a prevalence of 66% in 179 students in the USA.

A peaked (leptokurtic) and left-skewed distribution of mean spherical equivalent refractive error was present for all cohorts. The adult data were significantly more skewed than in the other groups, while kurtosis was significantly higher for the six to seven year old children. These refractive findings are consistent with reports that there is a departure

from a Gaussian distribution of refractive error, with a clear leptokurtic distribution evident by the age of six years (French *et al.*, 2012; Mutti *et al.*, 2005; Ojaimi *et al.*, 2005; Watanabe *et al.*, 1999). Though a negative skew has been identified in adult populations, studies have consistently shown a positive skew in childhood, due to a higher prevalence of hyperopia (Flitcroft, 2014; French *et al.*, 2012). This was not the case for the children examined in this study, likely to be attributable to the higher proportion of myopia and markedly more myopic mean MSE than previous studies (French *et al.*, 2012; Ojaimi *et al.*, 2005).

Mean AXLs were longer than those reported by the SMS and NICER studies but comparable to those of the Zadnik *et al.*'s CLEERE study (2003). This is unsurprising as the prevalence and level of myopia was much more closely matched in the current study and CLEERE. A Gaussian distribution of AXL was present for all cohorts, consistent with SMS (French *et al.*, 2012) NICER (French *et al.*, 2012) and the work of Ojaimi *et al.* (2005). The skewness of AXL data was also similar to NICER and SMS (French *et al.*, 2012), these. The distribution of AXL in the six-seven years and 12 - 13 years groups showed some kurtosis (six - seven years = 0.85, adult group = 0.33), however was flatter in the 12 - 13 year old children (- 0.33). Conversely, SMS and NICER found lower levels in the 6 - 7 group and a higher level in the 12 - 13 year group (See Table 4.8) (French *et al.*, 2012).

	6-7 years			12-13 years		
	SMS	NICER	Current	SMS	NICER	Current
MSE (D)	+1.40	+1.41	+0.87	+0.83	+0.66	-0.66
MSE kurtosis	15	7.2	13.5	19.5	5.9	3.6
MSE skew	2.5	2.2	-0.9	0.3	1.2	0.14
AXL (mm)	22.58	22.51	22.70	23.24	23.30	23.49
AXL kurtosis	0.38	0.40	0.85	1.22	1.72	-0.33
AXL skew	-0.2	-0.3	-0.1	0.00	-0.1	0.3

Table 4.8 Comparison of MSE and AXL between children living in Australia (SMS), Northern Ireland (NICER) and England (current study). Data for SMS and NICER redrawn with data from French *et al.*, 2012. [Comparison of refraction and ocular biometry in European Caucasian children living in Northern Ireland and Sydney, Australia, French, A. N., O'Donoghue, L., Morgan, I. G., Saunders, K. J., Mitchell, P. and Rose, K. Invest Ophthalmol Vis Sci. Vol 53, Copyright © The Association for Research in Vision and Ophthalmology, Inc.].

When data were analysed by gender, it was found that the eyes of females in both of the child groups had a significantly shorter AXLs than their male counterparts, despite there being no significant difference found between MSE. Though other studies of children have also found males to have longer AXLs than females, the discrepancy in the current study is larger, at 0.41 mm difference compared to the 0.23 mm and 0.32 mm difference in AXL found in previous studies (Gwiazda *et al.*, 2002; Zadnik *et al.*, 2002). No difference was found for AXL in the adult group, however, females had significantly more myopic MSEs than males. This differs from previous work, which has found no significant difference in MSE, but that females have significantly shorter AXLs than males (Logan *et al.*, 2005).

The correlation coefficient for the relationship between AXL and MSE became stronger for each increasing age group and were as follows; age six - seven = - 0.37, 12 - 13 = - 0.48 and adult = - 0.68. The COMET study (Zadnik *et al.*, 2002) and a study by Jensen (1991) found correlation coefficients of - 0.32 and - 0.49 respectively. However, these were not broken down into age categories (COMET, 6 - 11 years, Jensen, 6 - 12 years) as in the current study. The ranges also differed, with these studies only examining myopic subjects (COMET = - 1.25 D to - 4.50 D, Jensen, - 1.25 D to

- 6.00 D). Zadnik *et al.* (2002) stated differences in the range of refraction as the reason for these differences in correlation between the two studies. SMS, NICER (French *et al.*, 2012) and Ojaimi *et al.* (2005) have also shown significant correlations between AXL and MSE in child populations.

From the dioptric values of the regression slopes (see Section 4.3.4), it would appear that in childhood, 1 mm of axial expansion has a more profound effect on refractive error than in an adult population. It would also seem that the effect is more marked for the younger (six - seven years) than the older (12 - 13 years) children. This finding is coincident with an elongation of mean AXL as the cohorts increase in age, and is likely a reflection of the predicted reduction in Rx: AXL ratio forecast by the optical modelling presented earlier in this Chapter (see Section 4.1 and Table 4.1). This is further supported by the DTA described in Figure 4.5 which found refractive error to be the most significant influence on Rx: AXL ratio in this study.

The AXL: Rx values of 0.33 mm/D and 0.35 mm/D given for adult participants in the studies of Deller *et al.* (1947) and Atchison *et al.* (2004) are most closely matched to the value for the 12 - 13 year old cohort in this study (0.32 mm/D). The adult value was longer than this (0.40mm/D) and the six - seven year old value shorter (0.28 mm/D). It is clear that estimations made for the change in eye size per dioptre increase in myopia are related to the distribution and magnitude of myopia in a population. A value of three millimetres of axial elongation per dioptre of myopic error taken from studies of adult populations such as those of Deller *et al.* (1947) and Atchison *et al.* (2004) is commonly used as a clinical approximation to help to understand and estimate the link between AXL and MSE. The findings of this study lead us to make the recommendation that caution should be taken when applying these assumptions to populations with different refractive characteristics, as one standard approximation figure is not universally applicable and is

not necessarily representative, given the changing prevalence of refractive error with ocular development and growth. Instead, an appropriately matched figure should be used. The Rx: AXL ratio values presented in the present study are of particular use, as in terms of age and refractive distribution they are representative of populations which are commonly used in myopia control investigations. The failure to use appropriate figures to approximate the efficacy of myopia control interventions has the potential to either obscure or overestimate the effect of the treatment modality in question.

This study found that gender and ethnicity had no influence on the AXL: RX ratio (both DTA, $p > 0.05$). This suggests that despite known differences in the prevalence of myopia that are known to occur alongside these demographic characteristics the mechanism by which the myopia is occurring in these cases is the same. Ocular growth and refraction are dynamic and change irregularly over the period leading to ocular maturity (Ojaimi *et al.*, 2005; Sorsby and Leary, 1969). Alongside axial expansion, changes in refractive components have been shown to occur during this period. This fluidity in the coordination of ocular components may be sufficient to cause dissimilar relationships between AXL and refractive error in eyes at different stages of development. Longitudinal (Pennie *et al.*, 2001) and cross-sectional studies (Mutti *et al.*, 2005) have shown that in terms of refraction and ocular growth, the older eye cannot be considered as a simple scaled up version of the infant eye. However the only way of truly understanding the interplay between refractive error and axial length change is to examine it by means of a longitudinal study designed to following a large cohort of children, with a wide range of refractive errors over a long time frame encapsulating emmetropisation to adulthood.

Charts for plotting physical characteristics such as height and weight ranges and comparing the data with normative centile ranges are widely used in primary and secondary paediatric care for the routine surveillance and monitoring of a child's

development. Future work to consider would be the development of similar charts but derived from normative AXL data such as the data presented in this chapter. Such charts may be a useful tool in an optometric or ophthalmological setting, particularly myopia control. As well as being an easy indicator of whether the ametropia was axial or refractive/index related (see Section 1.1.1), it may be beneficial to develop growth curves for AXL for children in the same way that we have height and weight charts for children. Extending this study to be longitudinal would also allow the development of such charts to include an adult AXL or refraction predictor comparable to those available for predicting adult height and stature currently. This may be of use when explaining and answering a parent's concerns and worries about myopia progression and end point of refraction. Another advantage of such a tool would be that the risk of myopia progression could be identified from a range of children with similar refractive characteristics.

5. THE INFLUENCE OF AGE, REFRACTIVE ERROR, ETHNICITY, GENDER AND AXIAL LENGTH ON CORNEAL AND REFRACTIVE ASTIGMATISM

5.1 Introduction

Astigmatism is a common refractive error (Huynh *et al.*, 2006) which is highly prevalent at birth. However, its prevalence greatly reduces by the age of two years old (Abrahamsson *et al.*, 1988; Gwiazda *et al.*, 2000; Gwiazda *et al.*, 1984; Hirsch *et al.*, 1963). Numerous associations have been made with astigmatism, including certain ocular diseases, ethnicity, genetics, ocular biomechanics, and spherical ametropia (Kee *et al.*, 2013; Lyle, 1991; Read *et al.*, 2007).

Despite the fact that astigmatism is common and degrades visual performance (Abrahamsson and Sjostrand, 2003; Flitcroft *et al.*, 2005; Harvey *et al.*, 2004; Lyle, 1991; Somer *et al.*, 2002), what causes astigmatism and whether it interferes with refractive development is unclear (Kee, 2013). Though a potential association between astigmatism in early life and myopia development has been postulated (Fulton *et al.*, 1982), there is significant paucity of prospective research data available on the changing profile of an individual's astigmatic ametropia during the school years (O'Donoghue *et al.*, 2015; Tong *et al.*, 2004). In addition, the role of astigmatism in emmetropisation is unclear (Gwiazda *et al.*, 2000) and whether it is a cause or an effect of ametropia development also remains unelucidated (Farbrother *et al.*, 2004; Kee, 2013; O'Donoghue *et al.*, 2015).

Numerous studies have reported on the prevalence of refractive astigmatism in children of school age (Dandona *et al.*, 2002; Gwiazda *et al.*, 2000; Harvey *et al.*, 2006; He *et al.*, 2004; He *et al.*, 2007; Hirsch, 1963; Huynh *et al.*, 2007; Kleinstei *et al.*, 2003; Mutti *et al.*, 2004; Naidoo *et al.*, 2003; O'Donoghue *et al.*, 2011; O'Donoghue *et al.*, 2015;

Villarreal *et al.*, 2000). However, reports of the levels in children with European ancestry have published widely differing prevalence figures. A prevalence of 26% was found in the United States CLEERE study (Kleinstei *et al.*, 2003) with a much lower prevalence of 6.7% reported in Australia (Huynh *et al.*, 2007) and Sweden (5.2%) (Villarreal *et al.*, 2000). The Northern Irish NICER study (O'Donoghue *et al.*, 2011) found that the prevalence of refractive astigmatism is stable between six and seven years and 12 and 13 years with prevalences of 24% and 20% found for each group respectively.

As well as studies presenting widely disparate figures on the prevalence of refractive astigmatism in childhood, there is also disagreement on whether, and if so, how refractive astigmatism changes throughout infancy (O'Donoghue *et al.*, 2011). Several studies have reported that the prevalence of refractive astigmatism increases throughout childhood (Dandona *et al.*, 2002; He *et al.*, 2007; Naidoo *et al.*, 2003), however He *et al.* (2004) found a decrease with age. Some studies have shown considerable change during childhood (Gwiazda *et al.*, 2000; Mutti *et al.*, 2004) whereas other cross-sectional and longitudinal reports have suggested that refractive astigmatism is relatively stable throughout later childhood (five to 15 years approximately) (Harvey *et al.*, 2006; Hirsch, 1963; Huynh *et al.*, 2007; O'Donoghue *et al.*, 2011; Kleinstei *et al.*, 2003). However, as these studies analyse data for cohorts as a whole it is not always clear what happens to an individual's astigmatic error over this period (O'Donoghue *et al.*, 2015).

Prospective cohort studies have demonstrated equivocal findings: an association has been found between astigmatism and the development of myopia in childhood (Gwiazda *et al.*, 2000; Hirsch, 1964) and myopia progression (Fan *et al.*, 2004; Grosvenor *et al.*, 1987; Parnissen *et al.*, 2015). However, a study monitoring myopia progression over a three-year period did not find an association between the magnitude of lower levels of astigmatism (≤ 2.00 DC) and myopia progression (Parnissen, 1991).

Few studies, except surveys of non-Caucasian populations (Hervey *et al.*, 2006) have examined the prevalence of astigmatism in childhood beyond the age of 12 to 13 years. The work of O'Donoghue *et al.* (2015) which followed-up the children participating in the 2011 NICER study, confirmed previous longitudinal (Hirsch, 1963) and cross-sectional (Huynh *et al.*, 2007; O'Donoghue *et al.*, 2011) studies which report that the prevalence of astigmatism remains relatively stable throughout childhood and also demonstrates that prevalence of astigmatism remains constant after 12 to 13 years of age. However, the authors state that these prevalence data are misleading as results from the 2015 study showed that there was a notable minority of participants whose astigmatic profiles are dynamic rather than static within this period. Their study also found that the three year incidence of astigmatism in the younger cohort of the study was 11.6% and as such was very similar to that found for children in a similar age bracket in Singapore (Tong *et al.*, 2004). They also found that astigmatic errors ≥ 1.00 DC are likely to develop in approximately 10% of children during their early teenage years (O'Donoghue *et al.*, 2015).

The degree and axis of astigmatism have also been put forward as being possible factors in how astigmatism changes with age (O'Donoghue *et al.*, 2011) with some papers reporting that astigmatism in myopes increases whereas astigmatism in hyperopes decreases with age (Shih *et al.*, 2004; Tong *et al.*, 2004). There are also reports of increases in the prevalence of lower amounts of astigmatism (≤ 0.75 DC) but not higher levels of astigmatism (≥ 2.00 DC) throughout childhood (Dandona *et al.*, 2002; He *et al.*, 2007). O'Donoghue *et al.* (2015) found a weak association between increasing astigmatism and a hyperopic shift in the spherical component of the refraction in two cohorts of children (aged six - seven and 12 - 13 years at baseline) followed-up three years after enrolment (Spearman ρ younger cohort = 0.15, $p = 0.01$, Spearman ρ older cohort = 0.22, $p = < 0.001$). An association between increasing with the rule astigmatism

(see Section 5.3.2 for definition) and a myopic shift in refraction was also found, but for the older cohort only (Spearman $p = -0.31$, $p = 0.006$). However, as the correlation was low, neither the amount of astigmatism at phase one nor the change in astigmatism over the three year period are of use as clinical predictors of the change in the spherical component of refractive error over the same time frame (O'Donoghue *et al.*, 2015).

The prevalence of myopia is known to be population specific (Ip *et al.*, 2007). It is therefore hypothesised that similar patterns may be present in the distribution and refractive characteristics of astigmatism. This study aimed first to determine the prevalence of corneal and refractive astigmatism in two large, multi-racial groups of UK children, aged six to seven and 12 - 13 years, and one group of young adults, all from the metropolitan area of Birmingham, England. The influences of: axial length, refractive group, age, ethnicity and gender on corneal and refractive astigmatism (power and axis orientation) were investigated. Research questions are: (a) Do demographic or refractive parameters influence these forms of astigmatism in healthy eyes? (b) What are the normative variations? The findings will be discussed in terms of previous works on astigmatism in both UK and non - UK studies.

5.2 Ethical considerations

Ethical approval was granted by Aston University Research Ethics Committee. The research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from adult participants and each child's parent or guardian before participation in the study.

5.3 Methods

Data from two cohorts of children, taken from the Aston Eye Study (AES), and one cohort of Aston University students aged 18 - 25 years were analysed. These cohorts are the

same as those analysed in Chapter 4 of this thesis. See Section 4.2.1 for details of participant recruitment. This study again is an analysis of data previously collected by Dr Parth Shah and colleagues for AES and by Dr Nicola Logan at Aston University, Birmingham.

Participant numbers vary slightly from those described in Chapter 4 due to participants being excluded from this analysis owing to missing corneal curvature data. For participant numbers and demographics for this study see Table 5.1.

	Number	Age (years)		Ethnicity (%)		Gender (%)	
6-7 years	336	Mean	7.2	South Asian	61.6	Female	Male
		SD	0.30	White	19.0		
		Range	6.1 to 7.9	Black	12.5		
12-13 years	293	Mean	13.1	Mixed	4.5	48.5	51.5
		SD	0.30	Other	1.8		
		Range	12.3 to 13.8	East Asian	0.6		
18-25 years	117	Mean	20.5	South Asian	84.6	Female	Male
		SD	1.86	White	7.7		
		Range	18.4 to 25.8	Black	2.6		
				Other	2.6	54.7	45.3
				Mixed	1.7		
				East Asian	0.9		

Table 5.1 Cohort demographics by age group

For child participants, both eyes were cyclopleged prior to participation with one drop of Cyclopentolate Hydrochloride 1% (minims ® single dose, Bausch & Lomb, <http://www.bausch.co.uk>). One drop of Proxymetacaine Hydrochloride 0.5% (minims® single dose, Bausch & Lomb) was instilled prior to cycloplegia. A minimum of 30 minutes was waited between the instillation of Cyclopentolate Hydrochloride and commencement

of measures of refractive error. Confirmation of adequate cycloplegia was made by ensuring the presence of dilated pupils that were non-responsive to light, alongside an amplitude of accommodation of less than two dioptres.

Refractive error was measured with a binocular open-field autorefractor, with the participant fixating on a high-contrast maltese cross target at four metres from the autorefractor. An average of a minimum of three measurements was used for analysis. Measures of corneal curvature were taken using the Zeiss IOLMaster. The average of three corneal curvature readings was taken. Right eye data was used in analysis. For further details on cycloplegia, autorefraction and corneal curvature measurements and equipment see Chapter 2.

5.3.1 Sample size calculation

A priori power analysis was performed using G*Power 3 (Faul *et al.*, 2007). A two-tailed, linear bivariate regression (one group, size of slope) with an α level of 0.05 and a β level of 0.2 was performed to compute required sample size. Calculating for a medium effect size of 0.3 (Cohen, 1988; Prajapati *et al.*, 2010) resulted in a total required sample size of 82 in each group. Division by the asymptotic relative effectivity correction (ARE 0.91) for non-parametric data adjusted the sample size to a total requirement of 91 participants per group.

5.3.2 Definitions and statistical analysis

Mean Spherical Equivalent (MSE) refers to the spherical refraction plus half of the cylindrical refraction. Myopia was defined as $MSE \leq -0.50$ D, emmetropia as -0.50 D to $< +2.00$ D and hyperopia as $\geq +2.00$ D. All confidence intervals (CI) are 95%.

At present, there is no widely accepted definition of what level of astigmatism is classed as significant (O'Donoghue *et al.*, 2015). The American Association for Paediatric Ophthalmology and Strabismus Vision Screening Committee recommend that astigmatism of greater than 1.50 DC should be detected and corrected in children aged four years or older (Leat, 2011; O'Donoghue *et al.*, 2015). However, when surveyed, UK hospital optometrists reported that 50% of practitioners would consider prescribing for non-oblique astigmatism of ± 1.00 DC (Farbrother *et al.*, 2008). For the purposes of this study, astigmatism is classed as a cylindrical error of ± 1.00 DC or higher, without reference to cylindrical axis for prevalence analysis as this enables better comparison with previous prevalence data (Harvey *et al.*, 2006; Huynh *et al.*, 2006; Mutti *et al.*, 2004; O'Donoghue *et al.*, 2015; O'Donoghue *et al.*, 2011; Tong *et al.*, 2002). Astigmatism was grouped into prevalences of ≥ 1.00 DC, ≥ 1.50 DC and ≥ 2.00 DC. This classification was used as it was used to allow comparison with O'Donoghue *et al.*'s 2011 study.

Refractive astigmatism refers to the absolute cylindrical value taken from the autorefractor readings. Corneal astigmatism is taken as the difference between the flattest and steepest corneal meridian taken from the IOLMaster keratometry readings when the axis of astigmatism is taken as the flattest meridian.

Though there is much variation between studies in the classification of astigmatism as WTR, ATR or OBL (Harvey *et al.*, 2006), for the purpose of this study, WTR astigmatism includes negative cylinder axes falling between one and 15 degrees and 165 to 180 degrees, and ATR is defined as axes between 75 and 105 degrees, while OBL astigmatism is defined as those with negative axes from 16 to 74 and 106 to 164 degrees. These criteria were chosen in order to make for easier comparison to other studies of refraction and astigmatism (O'Donoghue *et al.*, 2011; Fan *et al.*, 2004; Huynh *et al.*, 2007).

To facilitate the comparison between corneal and refractive astigmatism, the axes of astigmatism were converted into their power vector form (Thibos *et al.*, 1997) for both refractive and corneal astigmatism. Conversion was made by applying a Fourier transformation using the equations shown in Equation 5.1.

$$J_0 = -\frac{C}{2} \times \cos 2\alpha$$

$$J_{45} = -\frac{C}{2} \times \sin 2\alpha$$

Equation 5.1 Fourier transformation equations for the calculation of vectors J_0 and J_{45} from the spherocylindrical refraction form. C refers to cylinder power in negative form and α refers to cylinder axis (Thibos *et al.*, 1997).

Converting to vector form produces two values, termed J_0 and J_{45} . J_0 represents Cartesian astigmatism, that is, astigmatism with its axes set at 90 and 180 degrees. WTR astigmatism is represented by a positive J_0 value, and ATR is indicated by a negative J_0 value (Liu *et al.*, 2011). J_{45} , however, is representative of oblique astigmatism, where a cross cylinder is set at 45 and 135 degrees. A positive J_{45} indicates that the power is greatest in the 135 meridian, whereas a negative J_{45} indicates that the 45 degree meridian has the greatest power. When interpreting astigmatism in terms of power vectors, it may be helpful to note that cylindrical power is equal to two times the square root of the sum of J_0^2 and J_{45}^2 (Liu *et al.*, 2011).

Specific statistical analyses used in this Chapter are; chi-square testing, Mann - Whitney U analysis, Spearman rank - order correlation, Kruskal - Wallis H analysis and decision tree analysis (DTA) using the chi-squared automatic interaction detection (CHAID) method. DTA analysis has been explained elsewhere in this thesis (see Section 4.2.6). Although the methodology and the data input process is the same as explained previously, it should be noted that the DTAs described in Sections 5.4.5 and 5.4.7 also incorporated ANOVA analysis due to the numerical nature of some variables.

5.4 Results

5.4.1 Prevalence of myopia

The prevalence of myopia ($MSE \leq -0.50$ DS) was lower in six to seven year-old children (8.9%, CI, 5.9 – 12.0) compared with 12 to 13 year old children (26.6%, CI, 21.6 - 31.7). The prevalence in the adult group was 53.0% (CI, 44.0 - 62.0). Prevalences of hyperopia were as follows: six - seven years = 10.4% (CI, 7.2 - 13.7), 12 - 13 years = 3.41% (CI, 1.3 - 5.5), 18 - 25 years = 0.8% (CI, 0 - 2.4).

5.4.2 Prevalence of refractive astigmatism

The prevalence of refractive astigmatism (≥ 1.00 DC) was 12.5% (CI, 9.0 - 16.0) in six to seven year old children and 12.3% for the 12 - 13 year old children (CI, 8.5 - 16.1). The prevalence in the adult group was 19.7% (CI, 12.5 - 26.9).

See Figure 5.1 for a breakdown of prevalence by degree of astigmatic error. For all levels of astigmatism, there were no statistically significant differences between age groups in the prevalence of refractive astigmatism (all $X_2 = > 0.05$).

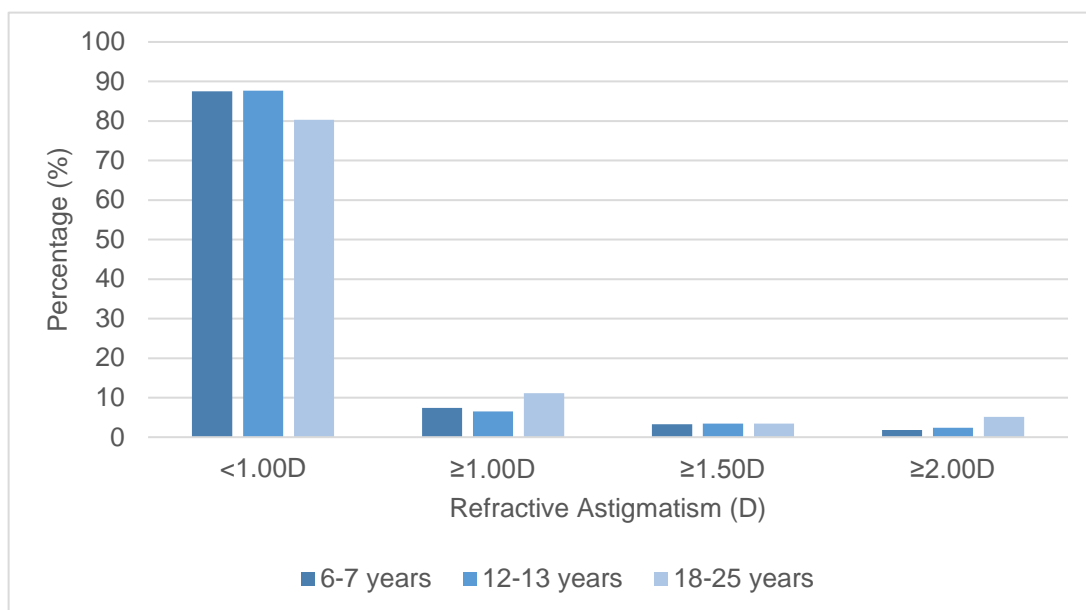


Figure 5.1 Prevalence of refractive astigmatism assessed with autorefraction. Comparison of six-seven year old children (n = 336), 12 - 13 year old children (n = 293) and 18 - 25 year olds (n = 117).

A chi-square test for association was conducted between age groups for the prevalence of refractive astigmatism over 1.00 DC. There was no statistically significant difference between groups ($X^2 (2) = 4.68, p = 0.10$).

5.4.3 Prevalence of corneal astigmatism

The prevalence of corneal astigmatism (≥ 1.00 DC) was 33.6% (CI, 28.6 - 38.6) in six to seven year-old children and 29.4% (CI, 24.1 - 34.6), in 12 - 13 year old children. The prevalence in the adult group was 48.7% (CI, 39.6 - 57.8).

See Figure 5.2 for a breakdown of prevalence by degree of corneal astigmatism. A significant difference between groups was found in the < 1.00 DC ($X^2 (2) = 14.04, p = 0.001$) and ≥ 1.00 DC ($X^2 (2) = 9.03, p = 0.01$) categories. For both levels over 1.50 DC, no statistically significant difference in the prevalence of corneal astigmatism between age groups was found (both $p = > 0.05$).

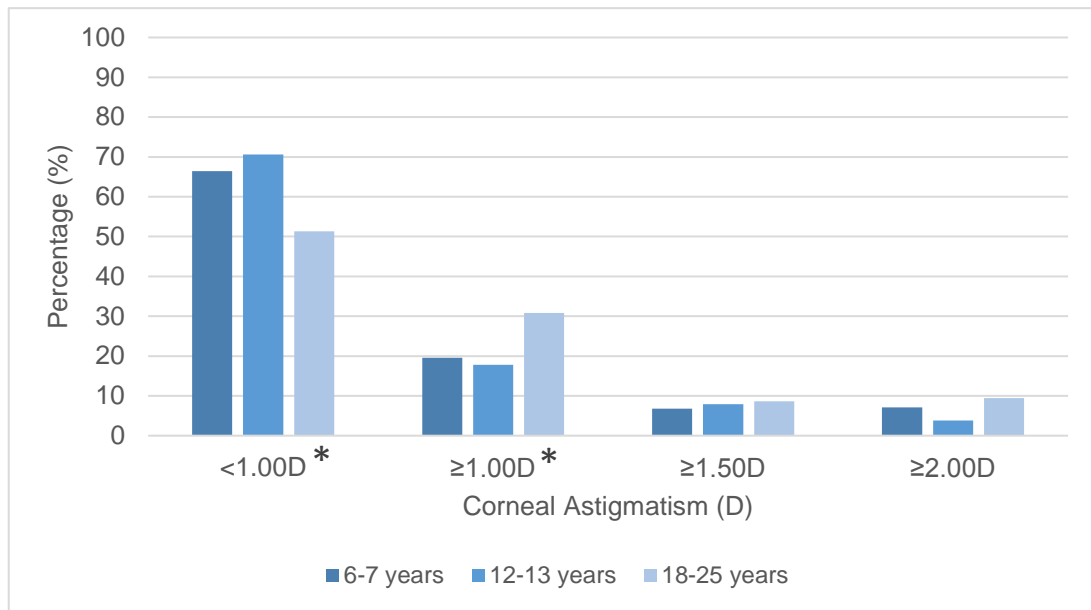


Figure 5.2 Prevalence of corneal astigmatism assessed with ocular biometry measures of corneal curvature. Comparison of six-seven year old children (n = 336), 12 - 13 year old children (n = 293) and 18-25 year olds (n=117). * denotes a significant difference in prevalence between age groups in these corneal astigmatism categories ($X^2 p < 0.05$).

5.4.4 Distribution and level of refractive astigmatism

Mann - Whitney U testing found no significant difference ($U = 47,701$, $z = -0.67$, $p = 0.50$) in median level of refractive astigmatism between age groups six-seven and 12 - 13 (age six – seven median level = -0.44 D, IQR = 0.39 , age 12 – 13 median = -0.45 D, IQR = 0.59). However, the distribution of refractive astigmatism between the adult group (adult median = -0.70 D, IQR 2.23) and the six - seven years group was found to be significantly different ($U = 21,976$, $z = -2.20$, $p = 0.03$), and also between the 12 - 13 year group and the adult group ($U = 18,972$, $z = 1.98$, $p = 0.05$).

5.4.5 DTA of factors influencing the level of refractive astigmatism

DTA of the dependent variable refractive cyclinder power is presented in Figure 5.3.

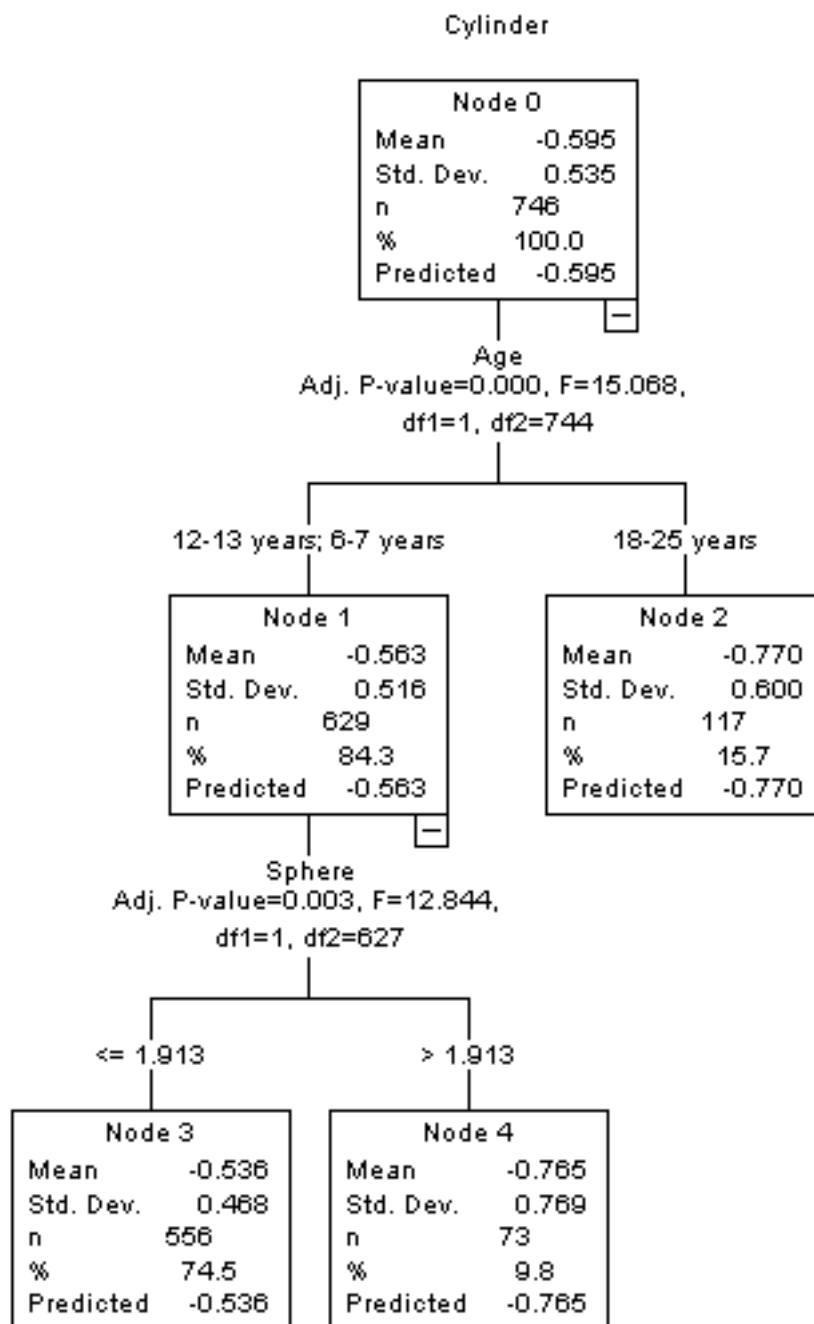


Figure 5.3 DTA of refractive astigmatism (cylinder) and the independent variables ethnicity, gender, age group, axial length and spherical error.

The DTA first differentiated the data on the basis of age at node one, with a higher mean level of refractive astigmatism reported for adult participants than for child participants (- 0.77 DC vs. -0.56 DC). Though there was no further splitting from the adult branch, the child node further differentiated on the basis of spherical error, with hyperopes over

+ 1.91 DS demonstrating a higher mean level of refractive astigmatism compared to participants with < + 1.91 DS of spherical ametropia (- 0.77 DC vs. - 0.54 DC). No significant associations were found for the variables ethnicity, gender or AXL (all $p > 0.05$).

5.4.6 Distribution and level of corneal astigmatism

When age groups were analysed separately by Mann - Whitney U analysis, no significant difference was found in the distribution of corneal astigmatism between the six - seven and 18 - 25 years age groups ($U = 22,137$, $z = 1.45$, $p = 0.15$). However, a significant difference in distribution was found when the six-seven year cohort was compared against the 12 - 13 years cohort ($U = 54,531$, $z = 2.33$, $p = 0.02$). There was also significant difference between the 12 - 13 and 18 - 25 year old cohorts ($U = 21,109$, $z = 3.06$, $p = < 0.005$). Median levels of corneal astigmatism were as follows: age six - seven median level = - 0.82 DC (IQR = 0.59), Age 12 - 13 median level = - 0.75 DC (IQR = 0.57), Age 18 - 25 median level = - 0.58 DC (IQR = 0.74).

5.4.7 DTA of factors influencing the level of corneal astigmatism

DTA analysis of the factors influencing corneal astigmatism found no significance for any of the independent variables (all $p = > 0.05$). Variables included in analysis were, age, gender, ethnicity and AXL.

5.4.8 Prevalence of refractive WTR, ATR and OBL astigmatism

Chi-squared testing found no significant difference in the prevalence of WTR refractive astigmatism (≥ 1.00 DC) between age groups ($X^2(2) = 4.01$, $p = 0.14$). However, the

proportions of ATR and OBL astigmatism were significantly different (ATR $X^2(2) = 11.57$, $p = < 0.005$, OBL $X^2(2) = 15.95$, $p = < 0.005$).

For the six to seven year old children, most refractive astigmatism was classified as oblique (61.9%, CI, 47.2 – 76.6). The proportion of WTR astigmatism was 26.2% (CI, 12.9 - 39.5), while the remaining 11.9% was ATR (CI, 2.1 – 21.7). For the 12 to 13 year old children, again most refractive astigmatism (≥ 1.00 DC) was classified as OBL (50.0%, CI, 33.7 - 66.3) WTR astigmatism proportion was 33.3% (CI, 17.9 - 48.7) ATR was 16.7% (CI, 4.5 - 28.9). For the adult cohort, again most refractive astigmatism (≥ 1.00 DC) was classified as OBL (65.2%, CI, 45.0 – 84.7). 30.4% had WTR corneal astigmatism (CI, 11.6 – 49.2) and 4.3% had ATR (CI, 0.0 – 12.6).

5.4.9 DTA of factors influencing the prevalence of WTR, ATR and OBL refractive astigmatism

DTA analysis is presented in Figure 5.4. The dependent variable was category of astigmatism (WTR, ATR and OBL) while independent variables were ethnicity, gender, age, axial length, absolute spherical error and cylindrical error.

The DTA bifurcates first on the basis of cylindrical error at the level of - 1.19 DC ($X^2(2) = 34$, $p = < 0.005$). Levels of astigmatism lower than this value are more likely to be OBL (64.1% vs. 47.3%). A further differentiation was identified within the subjects with cylinders under 1.19 DC on the basis of age, with a higher proportion of OBL astigmatism in the adult cohort than in either of the child cohorts ($X^2(2) = 14$, $p = < 0.005$). No association was found for the variables gender, ethnicity, axial length or spherical error ($p > 0.05$).

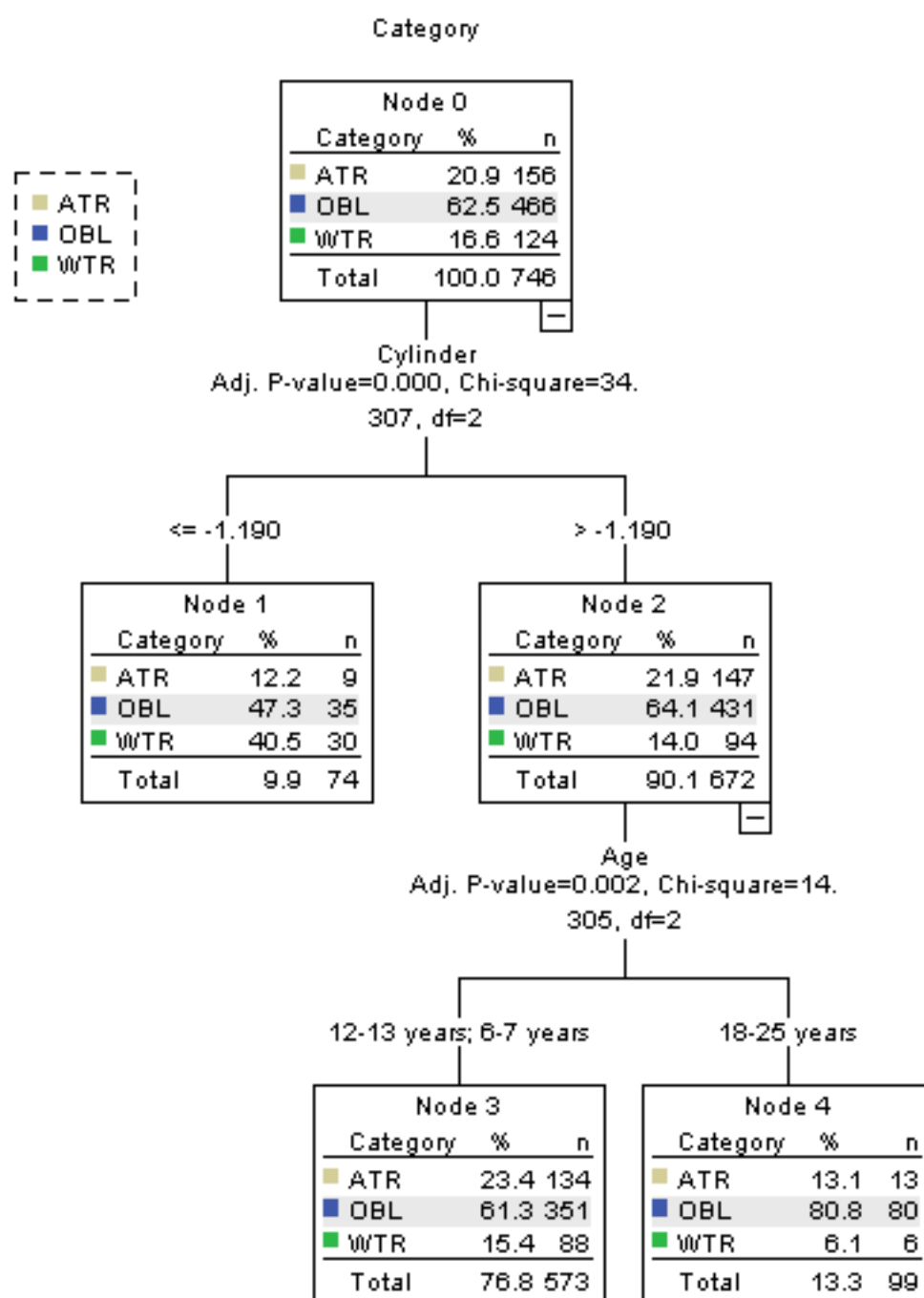


Figure 5.4 DTA of category of refractive astigmatism (WTR, ATR or OBL) and the independent variables ethnicity, gender, age group, axial length, spherical error and cylindrical error (cylinder).

5.4.10 Prevalence of corneal WTR, ATR and OBL astigmatism

Chi-squared testing found a significant difference in the prevalence of WTR, ATR and OBL corneal astigmatism (≥ 1.00 DC) when age groups were compared with each other (WTR $\chi^2(2) = 108.55$, ATR $\chi^2(2) = 171.90$, OBL $\chi^2(2) = 20.30$, for all categories $p < 0.005$).

Most corneal astigmatism (≥ 1.00 DC) in the six to seven year-old children was WTR (65.2% CI, 56.4 – 74.0), 2.7% was ATR (CI, 0.0 – 5.7) and 32.1% was OBL (CI, 23.5 – 40.8). In the 12- to 13-year-old children, 88.4% was WTR (CI, 81.3 – 95.2), 4.7% ATR (CI, 0.2 – 9.2) and 7.9% OBL (CI, 2.2 - 13.6). However, in the adult cohort, most corneal astigmatism (≥ 1.00 DC) was classified as ATR (84.2%, CI, 74.7 – 93.7). 14.0% had oblique corneal astigmatism (CI, 5.0 – 23.0) and 1.8% had WTR (CI, 0.0 – 5.3).

5.4.11 DTA of factors influencing the prevalence of WTR, ATR and OBL corneal astigmatism

The findings of the DTA can be seen in Figure 5.4. The DTA found the most significant difference was on the basis of age, with all 3 groups splitting separately ($\chi^2(4) = 341$, $p < 0.005$). All groups then bifurcated on the basis of absolute cylindrical power (see Figure 5.5 for statistical analyses). For both child groups the DTA identified an increasing prevalence of WTR astigmatism with increasing cylinder power, with the highest prevalences in the < -0.79 DC category (67.3%) for the six - seven year olds and in the < -1.05 DC category (91.9%) for the 12 - 13 year olds. ATR astigmatism became more prevalent with increasing cylinder size for the adult participants. The highest prevalence in adults was in the < -0.94 DC category, with a percentage of 84.7 %. Despite a further splitting on the basis of gender for children aged 6-7 with a cylinder of -0.80 DC to -0.34 DC, no other associations were found for gender, ethnicity or axial length ($p > 0.05$).

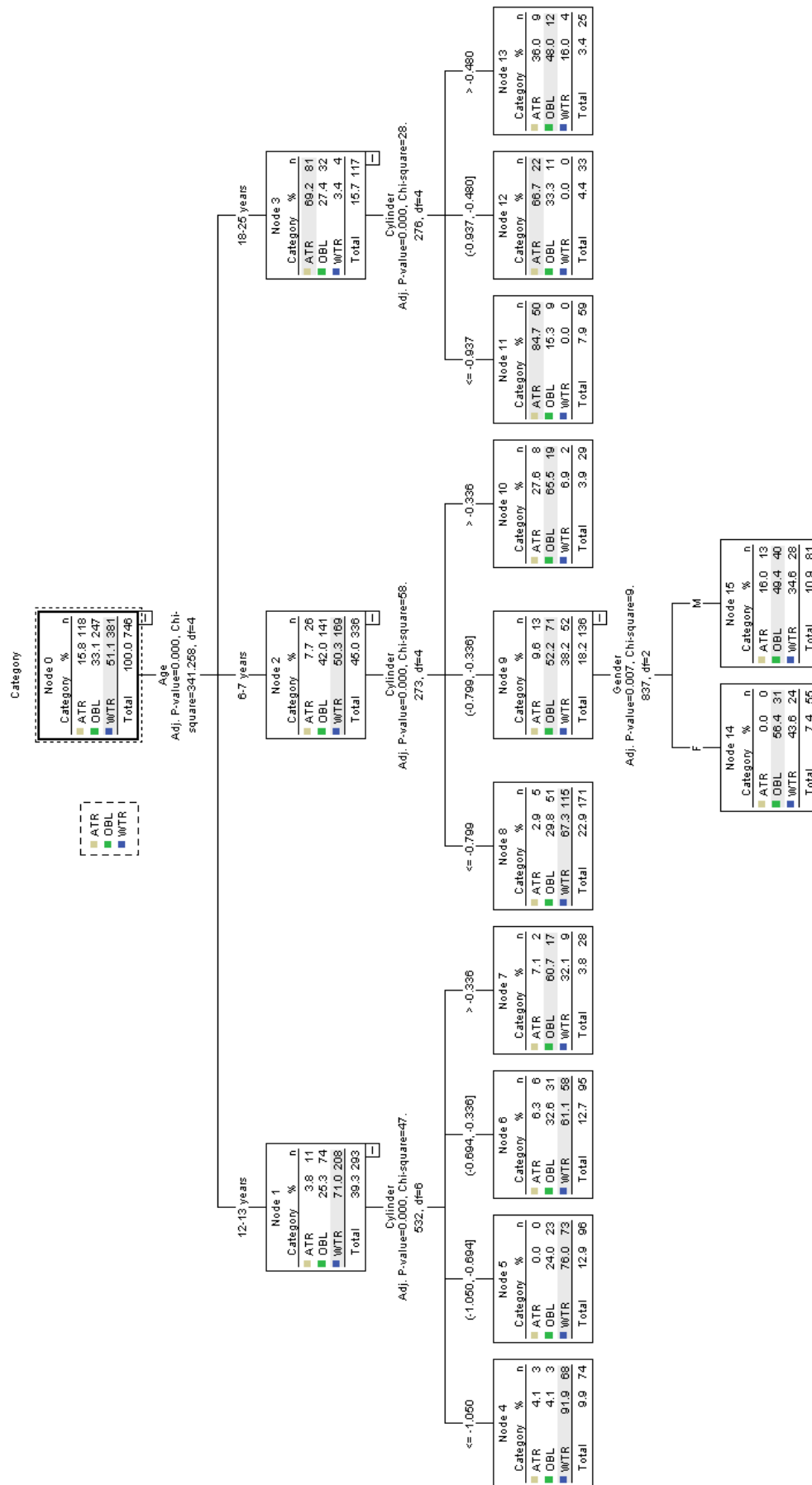


Figure 5.5 DTA of category of corneal astigmatism (WTR, ATR or OBL) and the independent variables ethnicity, gender, age group, axial length, and cylindrical error (cylinder).

5.4.12 Graphical representation of axes of astigmatism

However, as the classification of astigmatism into WTR, ATR and oblique has been described as rather arbitrary (O'Donoghue *et al.*, 2011), the distribution of the axes of both refractive and corneal astigmatism have been plotted in graphical form to better display the relationship between the magnitude and axis of astigmatism (for graphs of refractive astigmatism see Figure 5.6, Figure 4.4 and Figure 5.8) (for graphs of corneal astigmatism, see Figure 5.9, Figure 5.10 and Figure 5.11). These figures illustrate that for all groups, most refractive and corneal astigmatism is ≤ 2.00 DC.

In terms of refractive astigmatism, for all cohorts there is a fairly even distribution of the axes of astigmatism under 2.00 DC. The majority of refractive astigmatism over 2.00 DC are WTR. Apart from the six-seven years cohort, corneal astigmatism less than 2.00 DC shows a less even distribution than the axes of refractive astigmatism, with the majority of 12 - 13 year old participants having WTR corneal astigmatism, and the majority of 18 - 25 year old participants having ATR.

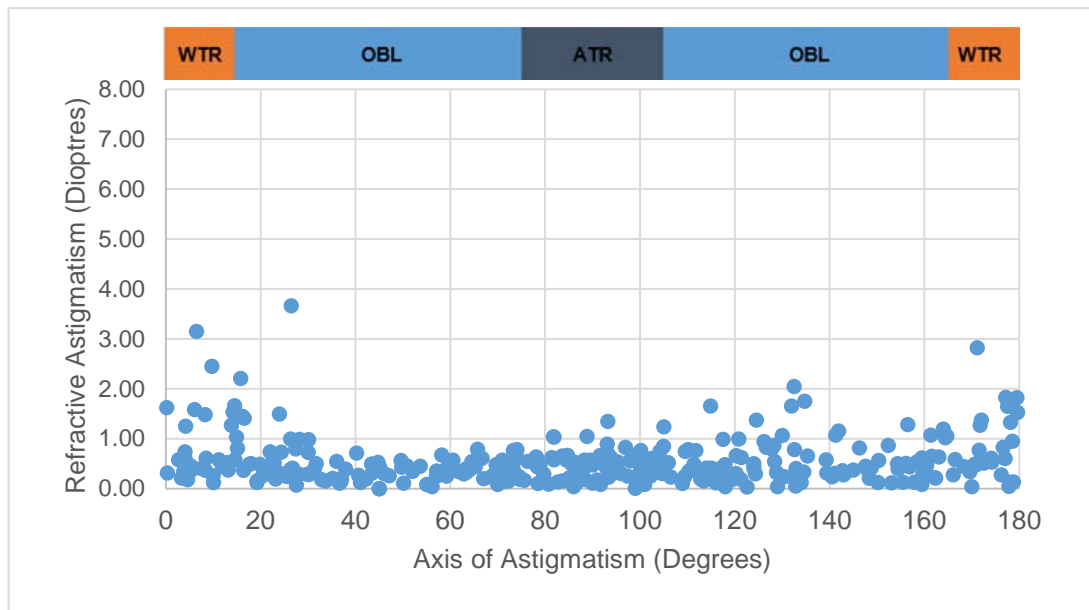


Figure 5.6 Plot of refractive astigmatism against axis of astigmatism for participants aged six - seven years (n = 336). The bar above the graph indicates which sections of the x-axis correspond to with the rule (WTR), against the rule (ATR) and oblique (OBL) astigmatism.

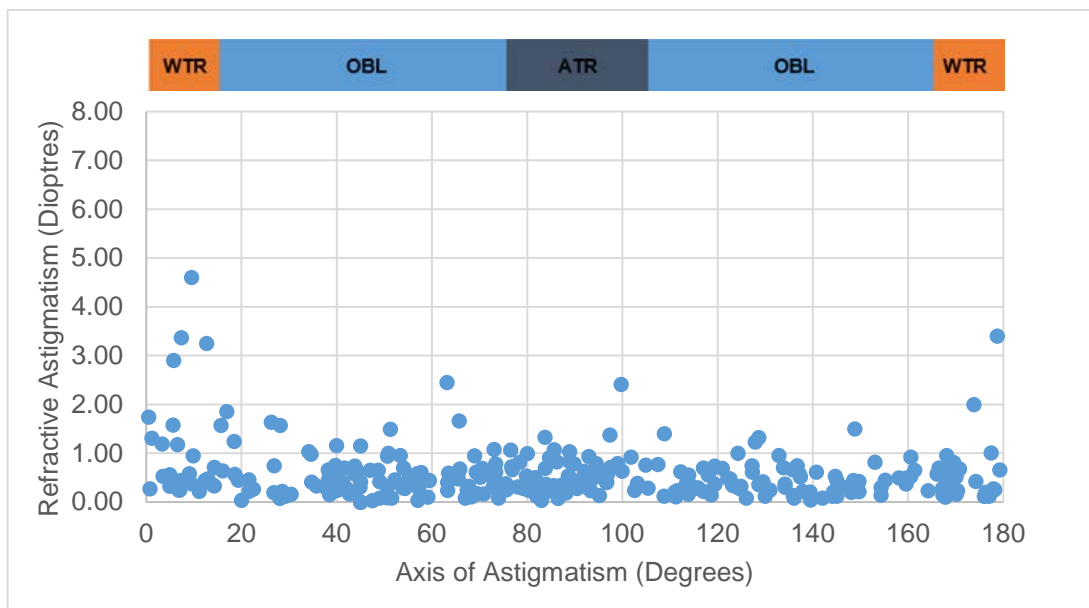


Figure 5.7 Plot of refractive astigmatism against axis of astigmatism for participants ages 12 - 13 years (n = 293).

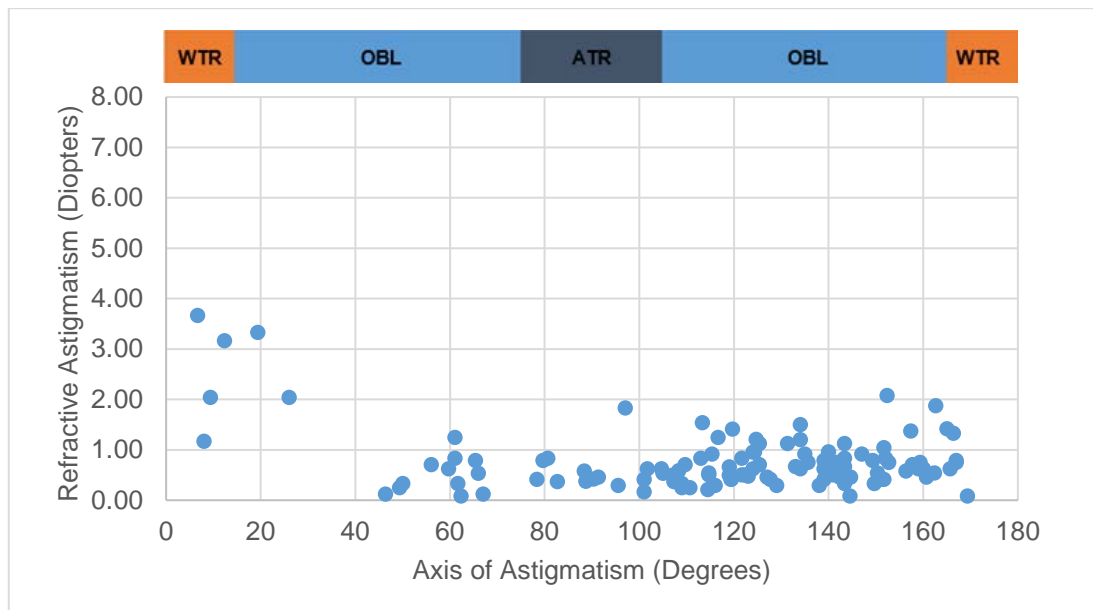


Figure 5.8 Plot of refractive astigmatism against axis of astigmatism for adult participants (n = 117).

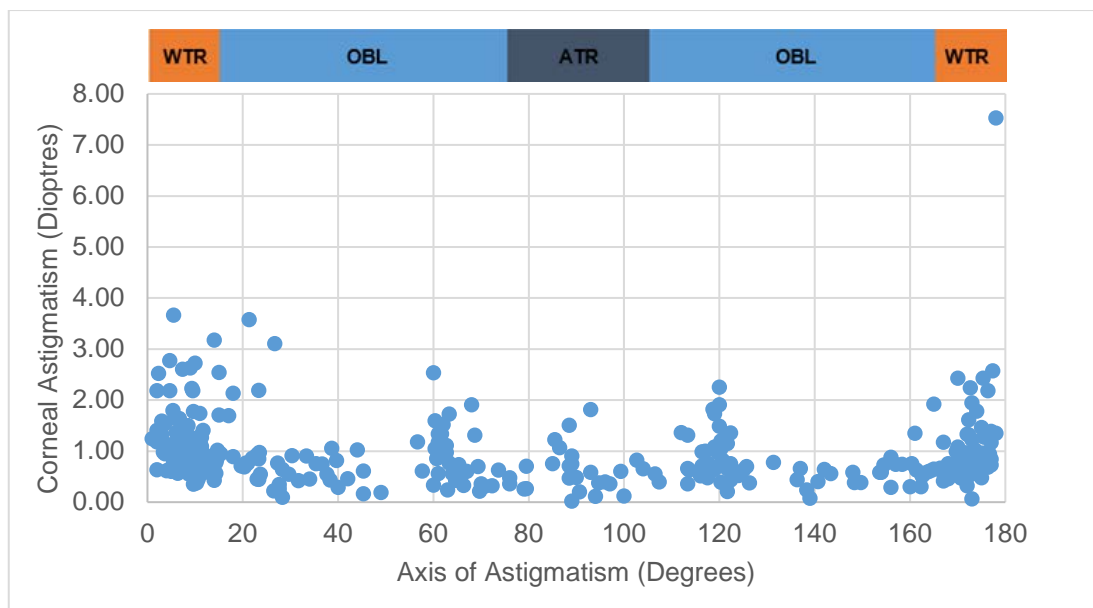


Figure 5.9 Plot of corneal astigmatism against axis of astigmatism for participants aged six - seven years (n = 336).

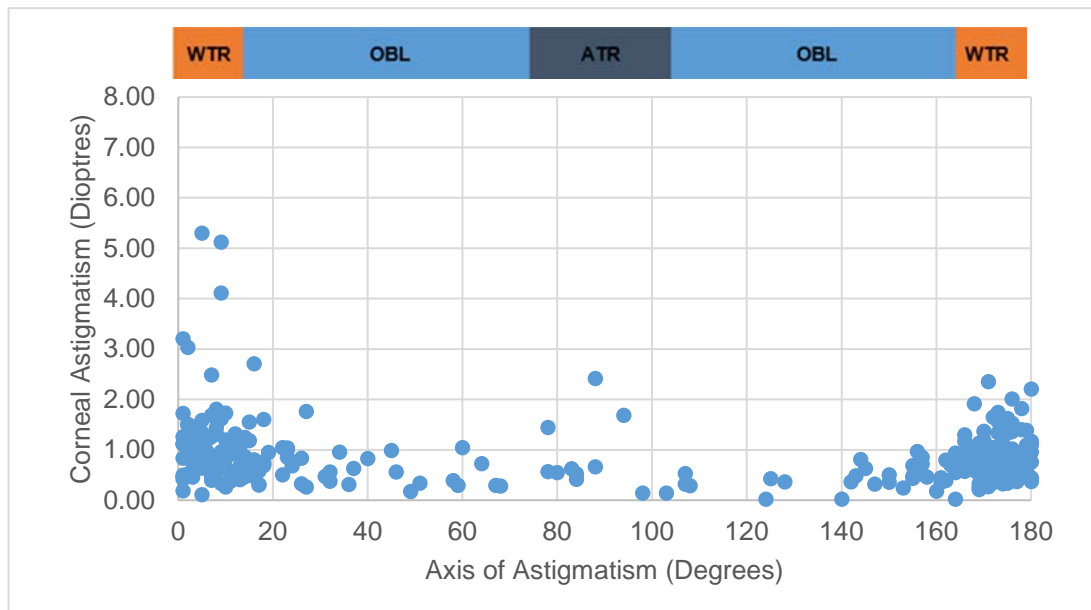


Figure 5.10 Plot of corneal astigmatism against axis of astigmatism for participants ages 12 - 13 years (n = 293).

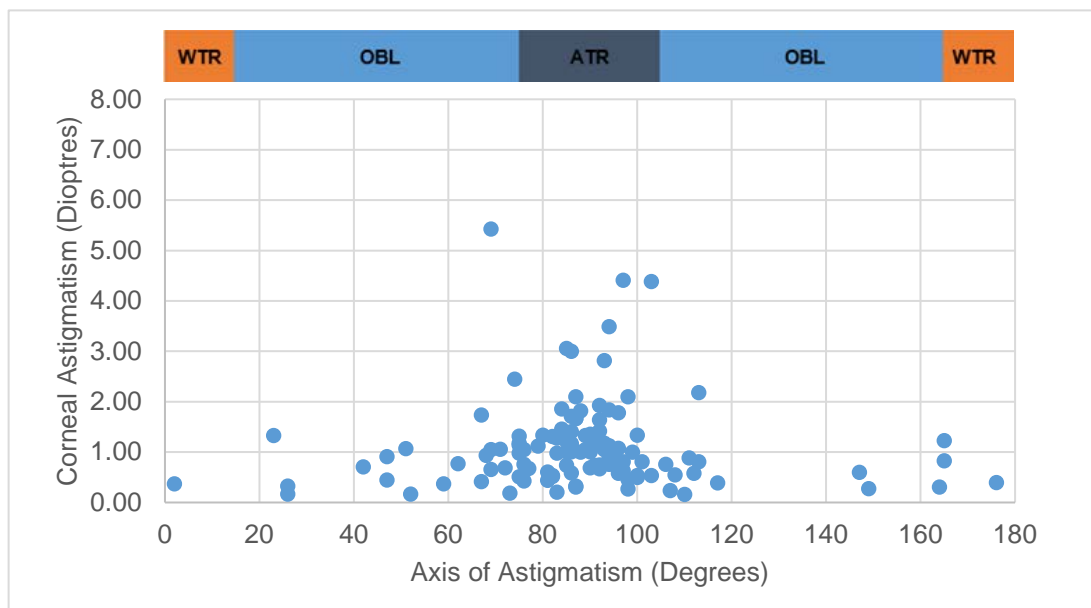


Figure 5.11 Plot of corneal astigmatism against axis of astigmatism for adult participants (n = 117).

5.4.13 Relationship between refractive astigmatism and refractive error

A statistically significant correlation was found between a greater amount of absolute refractive astigmatism and the absolute value of spherical refraction in the 12 – 13 year old age group (Spearman correlation, $r_s(291) = -1.76$, $p < 0.005$) (see Figure 5.13). However, no significant correlation was found in the six - seven year old cohort ($r_s(334) = -0.08$, $p = 0.17$) (Figure 5.12) or adult cohort ($r_s(117) = -0.15$, $p = 0.10$) (Figure 5.14).

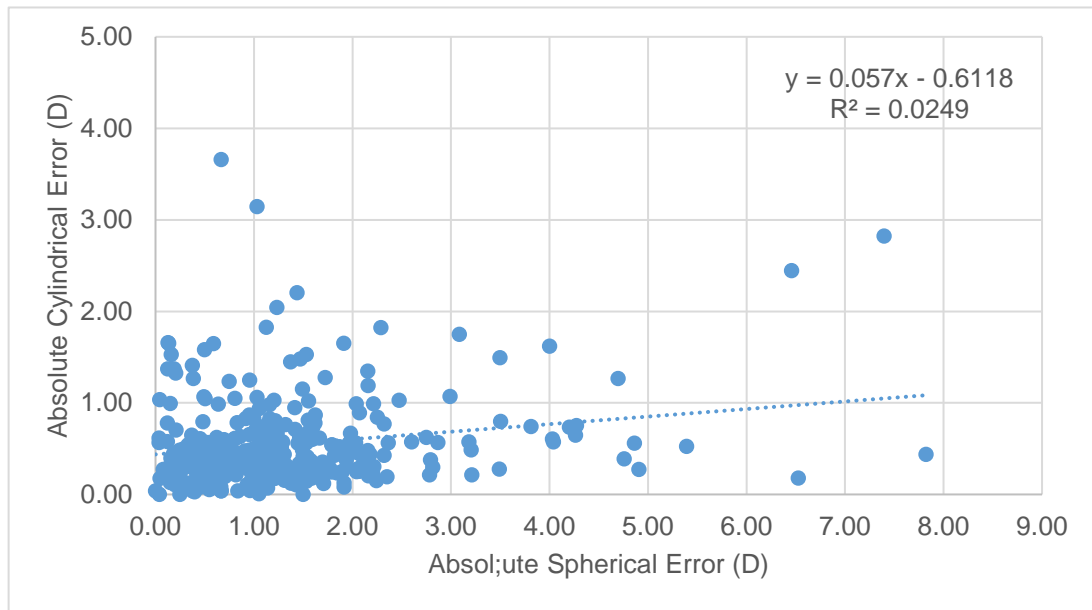


Figure 5.12 Relationship between absolute spherical refractive error and absolute cylindrical refractive error for the six-seven years old cohort (n = 336).

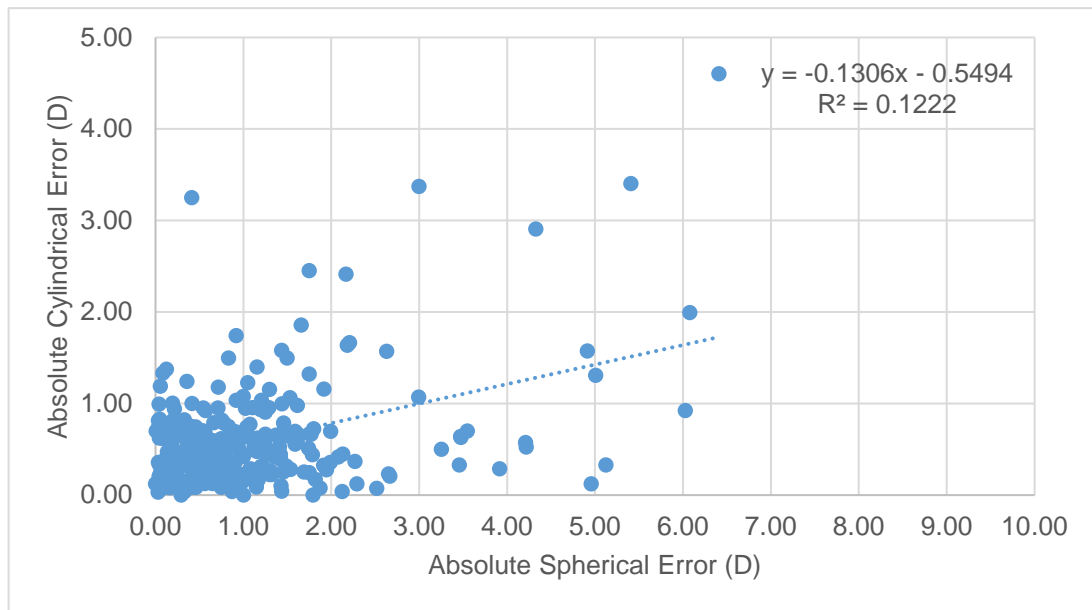


Figure 5.13 Relationship between absolute spherical refractive error and absolute cylindrical refractive error for the 12 - 13 years old cohort (n = 293).

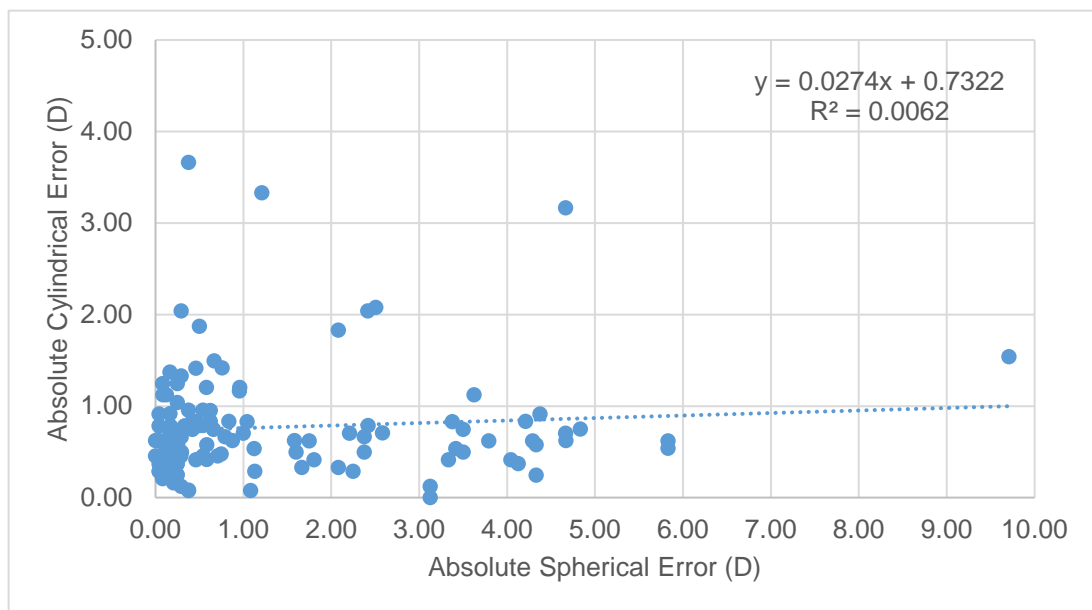


Figure 5.14 Relationship between absolute spherical refractive error and absolute cylindrical refractive error for the 18 - 25 years old cohort (n = 117).

Figure 5.15 illustrates that the presence of refractive astigmatism of at least 1.00 DC is most prevalent in children with refractive errors between + 0.50 D and +2.00 D whereas it is most prevalent in adults with spherical refractive errors in the range $\geq - 0.50$ D to $\leq + 0.50$ D.

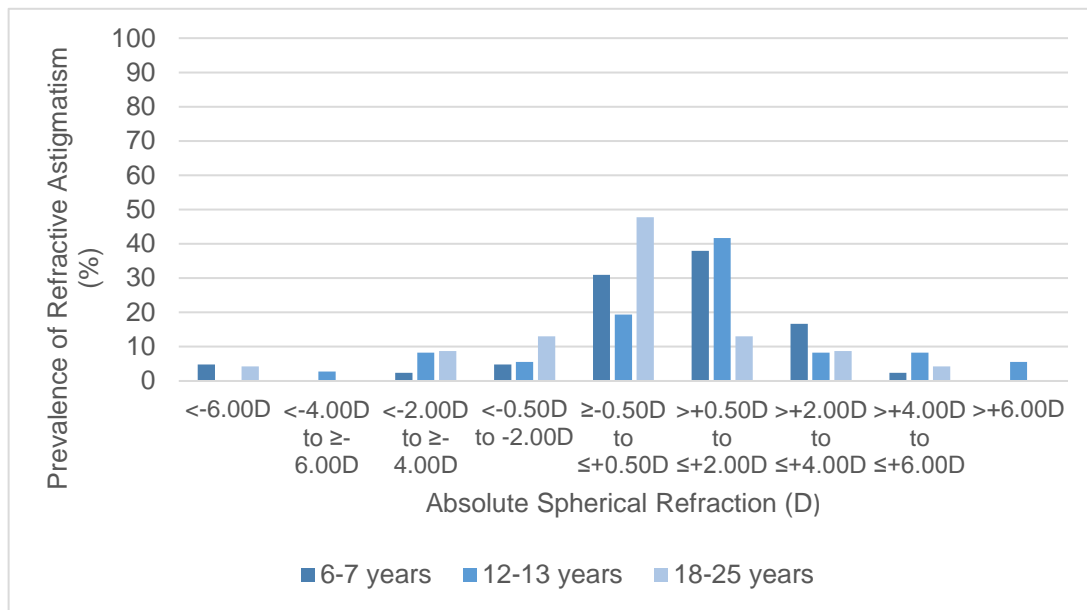


Figure 5.15 Distribution of refractive astigmatism $\leq 1.00D$ by absolute spherical refractive error category for children of 6 - 7 years ($n = 42$) and 12 - 13 years ($n = 36$) and adults aged 18 - 25 years ($n = 23$).

Kruskal - Wallis H analysis of all age groups found no statistically significant difference in the median level of absolute spherical error between the three axis classifications (WTR, ATR and OBL) (six - seven years $p = 0.71$, 12 - 13 years $p = 0.38$, 18 - 25 years $p = 0.30$). Similarly, no difference was found for the median level of MSE (six - seven years $p = 0.24$, 12 - 13 years $p = 0.33$, 18 - 25 years $p = 0.99$).

5.4.14 Relationship between corneal and refractive astigmatism

Figure 5.16, Figure 5.17 and Figure 5.18 show the correlation between corneal and refractive J_0 and J_{45} astigmatism for each cohort separately. Spearman rank - order analysis found no significant association between corneal and refractive J_0 or J_{45} for any age group (all $p = > 0.2$), except for the adult group for J_{45} , where a significant negative correlation was found ($r_s(293) = -0.23$, $p = 0.02$) (see Figure 5.18).

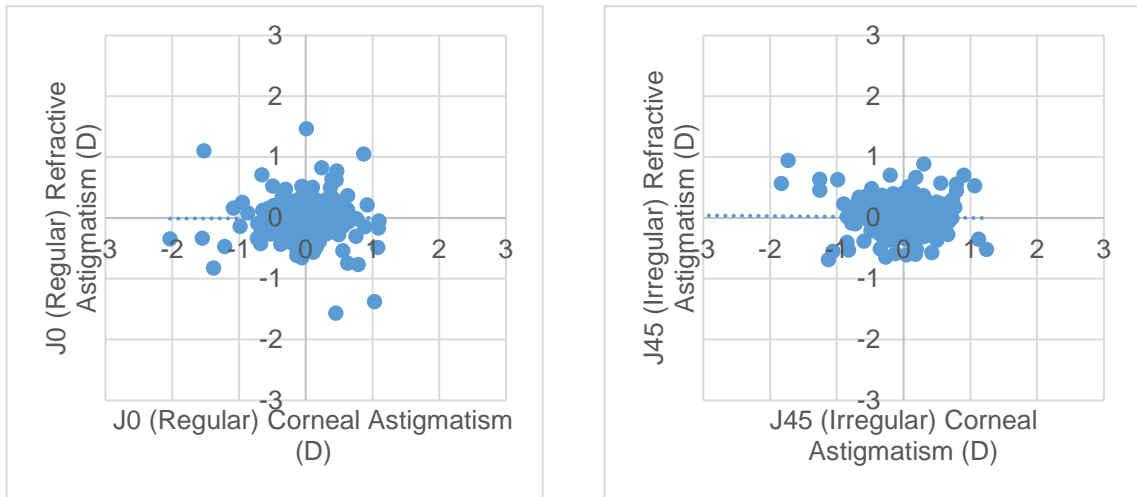


Figure 5.16 Relationship between corneal J_0 and J_{45} values for children aged six - seven years ($n = 336$).

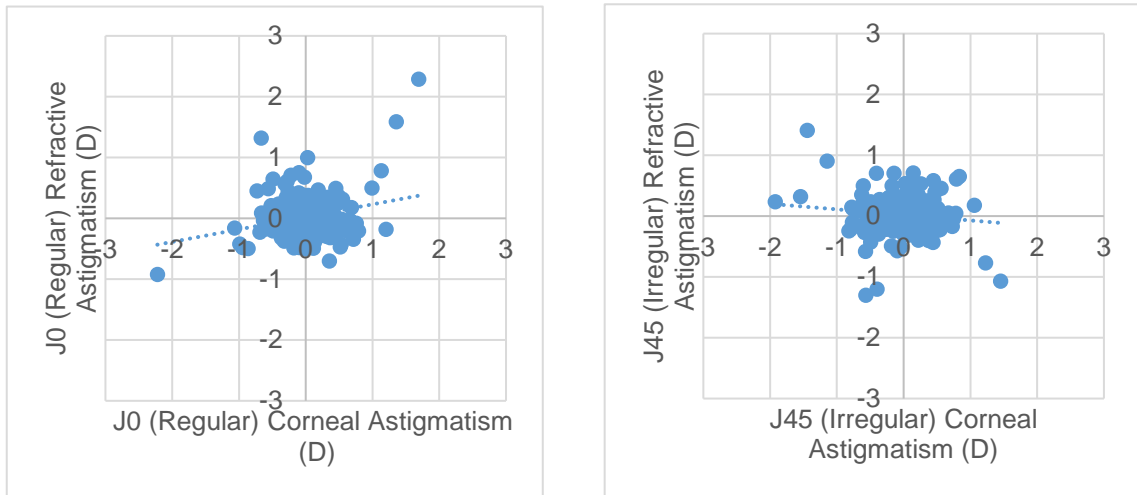


Figure 5.17 Relationship between corneal J_0 and J_{45} values for children aged 12 - 13 years ($n = 293$).

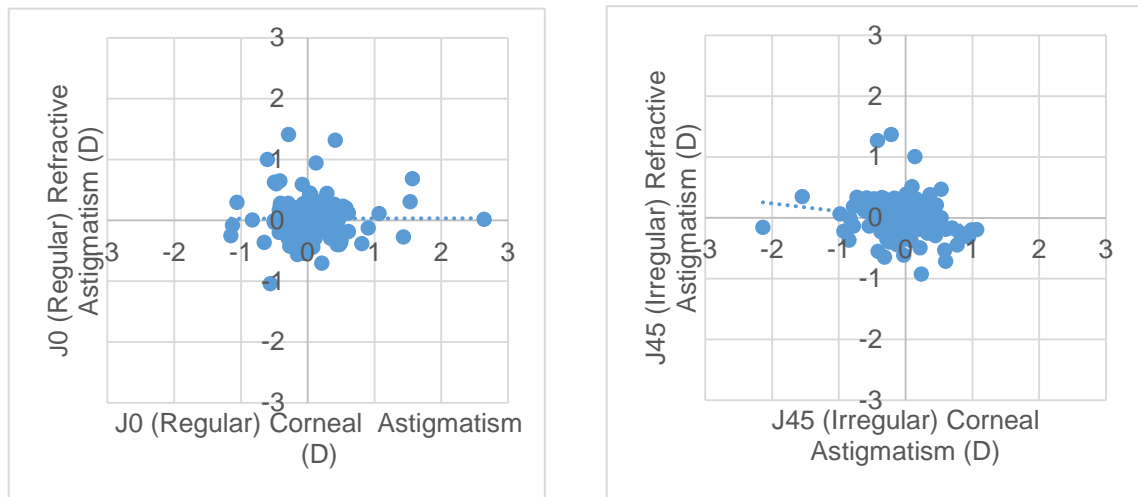


Figure 5.18 Relationship between corneal J_0 and J_{45} values for adults aged 18 - 25 years ($n = 117$).

5.5 Discussion

This chapter presents refractive and corneal astigmatism data collected from two groups of multi-ethnic, urban, UK children, aged six - seven years and 12 - 13 years old and one group of adult participants aged between 18 and 25 years. As in Chapter 4 of this study, which was based on approximately the same cohorts, the prevalence of myopia was found to increase between each consecutively older age group (six - seven years = 8.9%, 12 - 13 years = 26.6%, 18 - 25 years = 53.0%). The prevalence of myopia is considerably higher than that found in either the SMS or NICER studies (French *et al.*, 2012), but is more comparable to the USA CLEERE study which found a prevalence of 23.8% in 12 year old children (Mutti, D., oral communication, September 2011, as cited in French *et al.*, 2012). The prevalence of myopia in adults is consistent with previous cross-sectional studies of student populations (Fledelius *et al.*, 2000; Kinge *et al.*, 1998; Logan *et al.*, 2005).

No difference was found in the prevalence of refractive astigmatism of over 1.00 DC between age groups, which supports the findings of previous work that refractive

astigmatism appears to remain relatively stable between the ages of five and 15 years (Harvey *et al.*, 2006; Hirsch *et al.*, 1963; Huynh *et al.*, 2007; Kleinstein *et al.*, 2003; O'Donoghue *et al.*, 2011). Other, cross-sectional studies have however found an increase (Dandona *et al.*, 2002; He *et al.*, 2007, Naidoo *et al.*, 2003), or a decrease (Anstice, 1971; He *et al.*, 2004) in refractive astigmatism in this period. In the current study, no difference in the distribution of refractive astigmatism was found between the child cohorts, yet, both child cohorts were found to be significantly different from the adult distribution.

The data from the current study found the prevalence of refractive astigmatism (≥ 1.00 DC) to be 12.1% and 12.3% in the 6 - 7 and 12 - 13 year age groups respectively. This finding is approximately midway between the prevalences found in the similarly designed SMS (Huynh *et al.*, 2007) and NICER (O'Donoghue *et al.*, 2001) studies, which reported 4.8% in six year olds and 6.7% in 12 year olds (SMS) and 24.0% for six to seven year olds and 20.0% for 12 - 13 year olds in the NICER study.

The current study found a higher mean level of astigmatism in the adult cohort than the child cohort (DTA, - 0.77 DC adult cohort vs. -0.54 DC child cohort). For adults the highest prevalence of refractive astigmatism greater than 1.00 DC was found in the - 0.50 DS to + 0.50 DS category. However, for both child cohorts, the highest prevalence occurred in the + 0.50 DS to + 2.00 DS group. As all groups had a low prevalence of hyperopia it may be that there is in fact higher prevalences of astigmatism in the higher categories of spherical ametropia, however these are being masked by the low number of participants in these categories in this particular cross-section of the population. Interestingly, the NICER study which had a much higher percentage of refractive astigmats than this study also had a higher proportion of spherical hyperopes. This is supported by the DTA finding that child participants with hyperopias greater than

+ 1.91 DS also had higher cylindrical errors (- 0.77 DC vs. - 0.54 DC). This suggests that in childhood the degree of refractive astigmatism is linked more with hyperopia than myopia. This would also corroborate previous studies which have reported that hyperopic eyes are more likely to be astigmatic than myopic eyes (Baldwin and Mills, 1981; Dobson *et al.*, 2007; Garber, 1985). Although the exact reason for the difference found by these studies remains unclear, it may be that there is more potential for changes or reductions in astigmatism in myopic eyes as they are still growing and elongating. The DTA used in this study does, however, suggest that the degree of refractive astigmatism in children and adults does not appear to be influenced by variations of ethnicity, gender or axial length.

Studies have previously reported that corneal astigmatism exceeds refractive astigmatism (Grosvenor and Ratnakaram, 1990; Huynh *et al.*, 2006; Huynh *et al.*, 2007; O'Donoghue *et al.*, 2011). This was also the case for both child cohorts in this study, with both the prevalence (refractive astigmatism, six - seven years = 12.2%, 12 - 13 years = 12.3%, corneal astigmatism, six - seven years = 33.6%, 12 - 13 years = 29.4%) and magnitude (median refractive astigmatism, six - seven years = - 0.44 DC, 12 - 13 years = - 0.45 DC, median corneal astigmatism, six-seven years = - 0.82 DC, 12 - 13 years = -0.75 DC) of corneal astigmatism exceeding those of refractive astigmatism. In the adult cohort, 48.7% of participants had corneal astigmatism compared to 19.7% with refractive astigmatism, however, the median level of corneal astigmatism was lower (- 0.58 DC vs. - 0.70 DC). In the cohorts examined in this study no link was found between magnitude of corneal astigmatism and age, gender, ethnicity or axial length.

In this study, the majority of refractive astigmatism was oblique for all cohorts. This was also found in the NICER and SMS studies. However DTA analysis on our data further revealed that the categorisation of astigmatism as WTR, ATR or OBL is linked to the

level of cylindrical error. DTA identified that it is only refractive astigmatisms less than 1.19 DC which are more likely to be of oblique orientation. It has been suggested that oblique astigmatism varies significantly between geographical locations (Abrahamsson and Sjostrand, 2003). The same study reported that oblique astigmatism is a particular amblyogenic characteristic. However, similarly to the NICER study, graphical plotting of astigmatism showed the axes of astigmatism to be relatively evenly distributed, and in the cases of higher levels of astigmatism there was a tendency for it to be WTR or ATR. O'Donoghue *et al.* (2011) suggested that this may reduce the risk of developing astigmatic amblyopia in these individuals. The current study found that gender, ethnicity, axial length and spherical error had no influence on the categorisation of refractive astigmatism as WTR, ATR or OBL. Similarly, in terms of the distribution of axes of corneal astigmatism, DTA found no significant correlations on the grounds of ethnicity or axial length. Child participants showed an increase in the prevalence of WTR corneal astigmatism with increasing cylinder power while adults showed increasing ATR corneal astigmatism.

In the NICER study (O'Donoghue *et al.*, 2011) there was a correlation between change in refractive and corneal J_0 for both the younger and older cohorts. However, this was not the case for the J_{45} values, where change in refractive and corneal J_{45} only correlated in the younger cohort. In the current study, no correlation was found for any cohort for J_0 or J_{45} in the child populations. However there was a correlation for J_{45} in the adult group.

A limitation to this study is that the young adults were from a selected University population, so are not necessarily representative of a general population. However, the method of recruiting child participants means that the sample in these groups are representative of a school-age general, Birmingham population. As with the NICER study (O'Donoghue *et al.*, 2011), measures of corneal astigmatism in this study were made

solely on the basis of changes to the anterior curvature of the central cornea. It cannot be assumed that the posterior and peripheral curvature of the cornea or lens do not also contribute to the origin of astigmatism. Lens curvature is of particular interest as it has been proposed as a contributory source of myopic astigmatism, (Gwiazda *et al.*, 2000; Kaye *et al.*, 1997). Future studies would be strengthened by including measures of corneal topography and lens curvature.

6. A FEASIBILITY STUDY ON THE INVESTIGATION OF PERIPHERAL REFRACTION AND AXIAL LENGTH IN EYES WITH PERIPHERAL RETINAL DISEASE

6.1 Background

Although a great deal of research interest currently surrounds emmetropisation and the development of myopia, their mechanisms remain largely undiscovered (Flitcroft, 2012; Trolie *et al.*, 1992). The consensus belief is that the aetiology of myopia is multifactorial, with structural (Mutti *et al.*, 2005), environmental (O'Donoghue *et al.*, 2015) and genetic factors (Zadnik *et al.*, 2015) all playing a role in the determination of one's eventual refractive status. Nevertheless, the animal studies discussed in Section 1.7.2 of this thesis make it clear that eye growth has an actively regulated component that is vision dependent, alongside presenting significant evidence to suggest that the retina may be the pivotal structure in the creation of signals to guide refractive development (Schaeffel *et al.*, 1998; Wallman *et al.*, 1978).

Whether the human retina contains the discrete machinery to guide ocular growth remains undetermined (Schaeffel and Wildsoet, 2013). Findings from primate eyes are suggestive that a weighted importance of signals from separate retinal regions may exist, with most evidence seemingly suggesting that signals from the retinal periphery have a greater influence on the developmental mechanism (Sankaridurg *et al.*, 2011; Smith *et al.*, 2005; Smith *et al.*, 2007).

Myopia is not always an entirely benign, purely refractive condition. Studies have found that in 92% of cases of high myopia referred to a HES (Marr *et al.*, 2001) and 44% seen in a community optometry or orthoptic setting (Logan *et al.*, 2004a) high myopia is associated with an ocular or systemic morbidity.

It is as yet unclear to what extent studies manipulating emmetropisation in animal models apply to human ocular development, but it is obvious that it is an important mechanism to consider. Clinical observations of patients with discrete central or peripheral retinal anomaly, whether this is natural or iatrogenic, provides support for the idea that peripheral visual signals can significantly influence the emmetropisation process and resultantly the genesis of central ametropia. The study of patients with peripheral pathologies such as ROP and Retinitis Pigmentosa (RP) has shown that in these cases larger than normal ranges of central refractive errors and, on average, more significant central refractive errors are frequently exhibited (Connolly *et al.*, 2002; Knight-Nanan and O'Keefe, 1996; Nathan *et al.*, 1985; Sieving and Fishman, 1978) (see Figure 6.1).

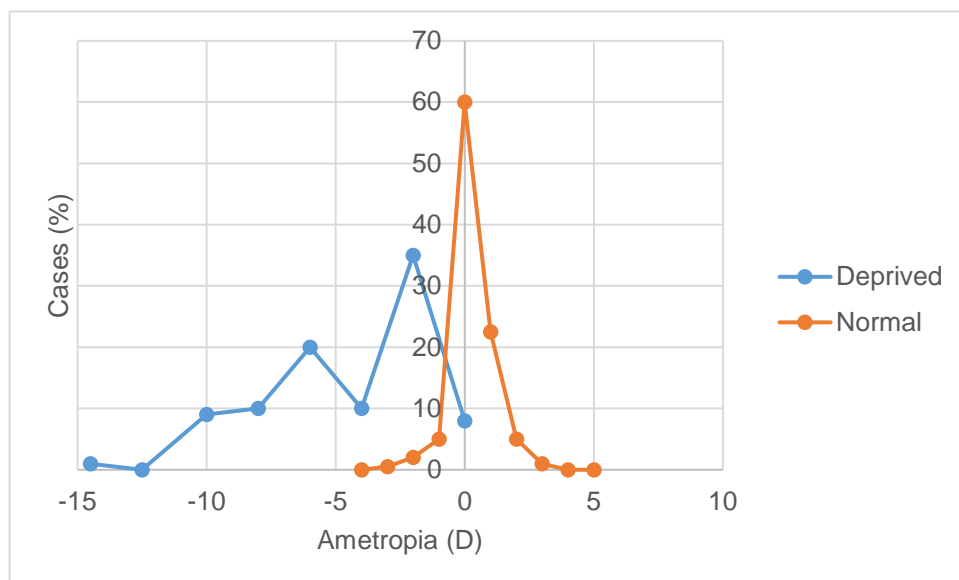


Figure 6.1 Distribution of refractive errors in healthy human eyes and eyes with ocular pathology. Redrawn from (Rabin *et al.*, 1981) [Emmetropization: a vision dependent phenomenon, Rabin, J., Van Sluyters, R. C. and Malach, R. Investigative Ophthalmology and Visual Science, Vol. 20, Copyright © 1981 Association for Research in Vision and Ophthalmology Incorporated].

In this respect, children who have pathologies primarily affecting the peripheral retina usually exhibit larger central refractive errors than children with primarily central anomalies (Nathan *et al.*, 1985). One potential mechanism by which these refractive

errors may be induced may be by interference from the abnormal retina with the signalling controlling emmetropisation.

Inherited retinal dystrophies are frequently associated with refractive errors (Chassine *et al.*, 2015), and several retinal dystrophies can be associated with myopia (Marr *et al.*, 2001). It should be noted that congenital dystrophies such as Leber's Congenital Amaurosis, are frequently linked to high hyperopias in the range of + 6.00 D to + 12.00 D, especially so in the very early forms of the condition (Hanein *et al.*, 2006). However, in retinal dystrophies that are not apparent at birth but onset in early life or later, for example RP, refractive error is significantly skewed towards moderate myopia and astigmatism (Francois and Verriest, 1962). A mean spherical error of - 1.86 D has been found in a population with RP in comparison with + 1.00 D in an age-matched population without eye disease (Sieving and Fishman, 1978). The precise mechanism of development, or the nature of myopia in these conditions is not understood.

This study presents a paradigm for the investigation of eye structure and function in the eyes of human children with certain retinal pathologies inspired specifically by the primate models of Smith *et al.*'s 2005 and 2007 studies (see Section 1.7.2). In these primate models visual input was altered in discrete retinal locations and the effect on axial length and refractive error measured using A-Scan Ultrasonography and Retinoscopy.

In Smith *et al.*'s 2005 experiment, a translucent goggle with a central aperture (24° or 37°) was applied bilaterally to 12 infant monkeys, depriving the peripheral retina of form vision while leaving central vision unrestricted. Regardless of unrestricted central vision, eyes which were peripherally deprived had more variable refractive errors and were significantly more myopic than controls (treated + 0.03 D \pm 2.39 D vs. control + 2.39 D \pm 0.92 D). Form deprivation myopia was found to develop to a comparable extent to eyes

in which vision in the entirety of the visual field was disrupted. Following the restoration of peripheral vision by diffuser removal, all eyes recovered from form deprivation myopia (Smith *et al.*, 2005).

Smith *et al.*'s following experiment (2007) disrupted the central retina (fovea and the majority of the perifovea – ten to 12° in diameter) of 13 infant monkeys exclusively, by rendering it non-functional by thermal laser ablation. Emmetropisation was either unaffected or form deprivation myopia developed. In cases where form deprivation myopia occurred, the eyes recovered comparably to intact eyes, despite the non-functionality of the fovea (Smith *et al.*, 2007).

Both studies (Smith *et al.*, 2005; Smith *et al.*, 2007) clearly indicate that signals from the fovea do not appear to be essential for many aspects of vision-dependent ocular development and that good central vision does not necessarily ensure normal refractive development. Also, peripheral visual signals can in isolation exert control over refractive development and result in large refractive errors if there is abnormal visual experience. It also appears that in cases of conflicting visual signals from the retinal centre and periphery, the peripheral retinal signals can dominate central development and ocular growth (Sankaridurg *et al.*, 2011).

Though these experiments are informative to emmetropisation and the development of ametropia in a primate model, it is unclear how applicable these findings are to the human eye. This study was designed with the primary aim of investigating refraction and biometry in children who have pathological damage of the central vs. the peripheral retina. It was hoped that this would explicate whether it is an appropriate and comparable model and similarities could be drawn with the findings of Smith *et al.*'s 2005 and 2007 primate studies. To ascertain the relative contributions of the central and peripheral retina in the developing eye, eye structure and function in children with normally developing

eyes were to be compared to children with certain retinal pathologies. It was hoped that this would advance the understanding of the role of the retinal periphery with regards to myopia development in humans and illuminate physiological and pathological variations in the structure of the human eye. Although current trials are attempting myopia amelioration by manipulating the peripheral image through modalities such as contact lenses, (Sankaridurg *et al.*, 2011) a deeper understanding of the characteristics of the developmental mechanism is necessary to underpin this work. As explained later in this chapter, the above aims of this study were hampered by difficulties with recruitment and as such the original aims became unachievable. Resultantly, this chapter, though still written to describe and give reference to the original study design and aims will be discussed in terms of a feasibility study and analysed with regard to whether the results from children with retinal pathology show grossly striking differences from children with normally developing eyes described in the previous chapters of this thesis.

6.2 Participants

This study aimed to recruit children aged five to 15 years and pathologies eligible were entirely retinal. Conditions that also affected other ocular structures were excluded from data collection. Conditions included in this study were retinal conditions affecting either only the central retina or only the peripheral retina.

For the purpose of this study, central conditions included any pathology that occurred within the retinal vessel arcades, and peripheral conditions were those where the damage was outside these blood vessels. Data were only collected in cases where the pathology had onset/been diagnosed at least six months before participation in the study. The following conditions are examples of those which were eligible for the study.

Central retinal pathologies that were considered for recruitment included but were not exclusive to: Retinoblastoma cases with small macular tumours, Stargardt's disease, Best Macular Dystrophy, other macular dystrophies and solar maculopathy.

Peripheral retinal pathologies under consideration were ones which fall outside the vessel arcades, for example, Congenital Stationary Night Blindness (CSNB), Familial exudative vitreoretinopathy (FEVR) without retinal traction, RP, and other peripheral retinal dystrophies.

Despite the varied range of conditions that were eligible for participation in this study, positive responses came only from participants with RP and CSNB. Therefore, only these conditions are described in Sections 6.2.1 and 6.2.2.

Four participants (one male and three females), of the age range eight to 15 years who had already been diagnosed with RP (two children) or CSNB (two children) participated in this study. These children were recruited via Birmingham Children's Hospital. MSE ranged from + 2.36 D to - 14.89 D (SD = 6.71). AXL ranged from 21.41 mm to 26.80 mm (SD = 2.00).

Axial length and refractive error data for healthy children with no current or previous history of ocular disease were used for comparison. These data were collected from six - seven year old and 12 - 13 year old Birmingham school-children participating in the Aston Eye Study and are described in detail in Chapter 4. There were 343 children in the six - seven years age group (mean age = 7.2 years, SD = 0.35). MSE ranged from + 7.60D to - 8.81 D (mean MSE = + 0.87 D, SD = 1.39). AXL ranged from 19.66 mm to 25.26 mm (mean AXL = 22.70 mm, SD = 0.78). In the 12 - 13 years age group there were 294 children (mean age = 13.1 years, SD = 0.32). MSE ranged from + 5.56

D TO - 5.66 D (mean MSE = - 0.06 D, SD = 1.42). AXL ranged from 20.56 mm to 26.09 mm (mean AXL = 23.49 mm, SD = 0.86).

For both age categories the majority of participants were of South Asian (six - seven years 61.2%, 12 - 13 years 38.8%) or white ethnicity (six – seven years 19.2%, 12 - 13 years 38.4%). See Section 4.2.3 for full ethnicity breakdown.

6.2.1 Retinitis Pigmentosa

Retinitis Pigmentosa (or rod-cone dystrophy) is the name given to a group of hereditary retinal pathologies that are characterised by degenerations of the rod and cone photoreceptors (Hartong *et al.*, 2006). In most typical cases of RP, the reduction in rod sensitivity is far in excess of the loss of cone function (Birch *et al.*, 1999). RP affects around one in four-thousand people worldwide and as such is the most frequent form of inherited retinal dystrophy (Chassine *et al.*, 2015). The most common inheritance of RP is in the autosomal recessive form, which is thought to account for 50 - 60% of cases. RP may instead be inherited as the autosomal dominant form in 30 - 40% of cases, or in the X-linked form in 10 - 15% of patients (Bunker *et al.*, 1984; Chassine *et al.*, 2015; Novak-Laus *et al.*, 2002).



Figure 6.2 Optomap image of the fundus of a patient with Retinitis Pigmentosa. Image courtesy of *BBR Optometry Ltd*.

The signs, symptoms and course of RP are highly variable. The age of onset of the disease is generally accepted to be the age at which a person begins to experience visual symptoms (Hartong *et al.*, 2006). In some cases, patients will experience symptomatic visual loss in childhood whereas in other instances, visual symptoms will not manifest until mid-adulthood. It is thought that the rate of disease progression may be influenced by the stage of the disease and dietary, environmental and genetic factors (Hartong *et al.*, 2006).

Visual field loss in RP is characterised by a progressive restriction of far peripheral and night vision in adolescence, which eventually advances to tunnel vision in young adulthood and finally results in a total loss of central vision, typically by the age of 60 (Hamel, 2006). These visual symptoms are due to the gradual loss of both the rod and cone photoreceptors. Attenuated retinal blood vessels is a universal finding in RP, whilst other observable fundus features are: bone spicule-shaped intra-retinal pigmentation in

the mid or far-periphery and optic disc pallor (Hartong *et al.*, 2006; Chassine *et al.*, 2015). However, these signs may both be absent in the early stages of the disease (Berson *et al.*, 1980). Other common findings are posterior subcapsular cataracts that occur in approximately 50% of RP cases (Berson *et al.*, 1980; Fishman *et al.*, 1985; Heckenlively, 1982; Pruett, 1983), and cells being present and observable within the vitreous humour (Hartong *et al.*, 2006). Though RP is usually confined to the eye, it should be noted that 30 syndromic forms exist which feature non-ocular disease, examples of these syndromes include Bardet—Biedl syndrome and Usher's syndrome (Hartong *et al.*, 2006).



Figure 6.3 Histological appearance of a healthy human retina (left) and retina of a patient with Retinitis Pigmentosa at a mid-stage of disease (right). The space between the retinal pigment epithelium and the outer nuclear layer in the diseased retina is a processing artefact. Reproduced with permission (Hartong *et al.*, 2006) [Retinitis Pigmentosa. Hartong, D. T., Berson, E. L. and Dryja, T. P. The Lancet, Vol. 368, Copyright © 2006, Elsevier Limited].

The outer nuclear layer of the retina is made up of rod and cone nuclei and is severely damaged in individuals with RP (see Figure 6.3). The inner nuclear layer remains fairly well preserved until the late stages of the disease when many of the amacrine, bipolar and horizontal cells begin to degenerate (Hartong *et al.*, 2006). The bone spicule pigmentation is deposited in the neural retina as a response to photoreceptor cell death

(Li *et al.*, 1995). Electroretinogram studies of patients with RP have found that in most cases, photoreceptor function has begun to degenerate many years before any visual symptoms are reported and as early as six years old, even in patients who do not report visual symptoms until early adulthood (Berson, 1993).

It should be noted that although in some individuals central field loss will occur in the initial stages of the disease, visual acuity may be of a normal level even in cases of advanced RP if a small central island of visual field remains. Patients can lose up to 90% of foveal cones before a reduction in acuity occurs (Gellar and Sieving, 1993). A visual acuity of + 0.10 LogMAR or better indicates the function of foveal cones (Holopigian *et al.*, 1996). However, patients who have a visual field restricted more than approximately 50 degrees in the horizontal meridian will begin to experience subjective difficulties with everyday tasks (Szlyk *et al.*, 2001). A decline in contrast sensitivity is common in RP (Lindberg *et al.*, 1981), and is often responsible for poor subjective vision in individuals who have a good high contrast resolution (Lodha *et al.*, 2003). Colour vision may or may not be affected. Acquired Tritanopia (a deficiency in blue cone function) is a classic finding in advanced RP (Hartong *et al.*, 2006).

Refractive error is significantly skewed towards moderate myopia and astigmatism in RP (Francois and Verriest, 1962). A study by Sieving and Fishman (1978) found an MSE of - 1.86 D in Retinitis Pigmentosa compared to + 1.00 D in a population without ocular disease. Interestingly, it was also concluded that there was a variance in refractive error between groups of RP patients with differing inheritance patterns. Individuals with X-linked Retinitis Pigmentosa were found to have significantly higher myopic refractive errors (mean MSE = - 5.51 D) than those with other forms of RP (mean MSE = - 1.20 D). Other studies have shown that X-linked RP is consistently associated with myopia (Jayasundera *et al.*, 2010; Pelletier *et al.*, 2007), and one study observed that X-linked

cases had average myopias over - 2.00 D (Fishman *et al.*, 1998). Conversely, autosomal dominant RP has been shown to be associated with hyperopic refractive errors (Berson *et al.*, 1980; Fishman *et al.*, 1988).

6.2.2 Congenital Stationary Night Blindness

CSNB describes a group of rare, clinically and genetically heterogeneous genetic disorders of the retina that predominantly affect signal processing within the photoreceptors, retinoid recycling in the RPE, or signal transmission via the retinal bipolar cells (Zeitz *et al.*, 2007). Fundus appearance may be normal or abnormal (Zeitz *et al.*, 2015).

A common visual symptom reported by individuals with CSNB is night or dim light vision disturbance or delayed dark adaptation due to impaired photoreceptor transmission; however, some patients also report photophobia (Zeitz *et al.*, 2015). Though night blindness is a common feature of many progressive retinal disorders, CSNB is present at birth and is a generally stable condition that does not feature RPE changes (Zeitz *et al.*, 2015). Some forms of CSNB may have other associated ocular findings such as; reduced VA, refractive error (most commonly myopia, but occasionally hyperopia), nystagmus, strabismus, and abnormalities of the fundus (Bijveld *et al.*, 2013, Miyake *et al.*, 1987). CSNB can be classified as X-linked, autosomal recessive or autosomal dominant, according to the pattern in which it is inherited (Carr *et al.*, 1974). ERG is an important diagnostic tool in CSNB (Zeitz *et al.*, 2015). Abnormal rod ERGs and an abnormal dark-adaptation curve are a universal finding in cases of CSNB (Godara *et al.*, 2012). X-linked CSNB can be further sub-divided into two forms, complete (also known as CSNB1) and incomplete (CSNB2). Though both forms of X-linked CSNB have similar signs and symptoms, the incomplete form is less severe, not always associated with

night blindness and there is a reduced but measurable rod cell response to light, whereas the response is absent in the complete form (Bijveld *et al.*, 2013). Oguchi disease is a distinctive form of autosomal recessive CSNB with an abnormal fundus appearance (Oguchi, 1907).

6.2.3 Exclusion criteria

This study had a variety of different exclusions, ranging from medical reasons to potential difficulty in performing the tasks. Participants were ineligible for participation in the study if they had poor general health or a systemic general health problem. This criterion also encompassed individuals with collagen/connective tissue disorders, for example, Marfan or Stickler syndromes.

Ocular reasons for being excluded included any ocular comorbidity inclusive of cornea, media or lens pathologies. Participants with surgically induced ametropia or those who had had previous refractive surgery were also excluded. Additionally, participants who were at the time of the study or have previously been involved with medicinal trials or refractive intervention (e.g. myopia control) studies were excluded.

Individuals who were born more than eight weeks prematurely were excluded. Long-term studies of refractive error have shown that there is a higher frequency of myopia in these patients compared to babies carried to full term (Choi *et al.*, 2004; Holmstrom *et al.*, 1998). Participants who are unable to perform the tests for example due to poor fixation or an inability to place their chin on a headrest were also excluded.

6.3 Methods

Data were collected from both eyes. A short ocular and general health history encompassing inclusion/exclusion criteria was taken before the measurement to ensure

participant eligibility. Distance VAs were recorded in LogMAR notation using an illuminated 4m ETDRS chart (Precision Vision, La Salle, IL, USA). For participants who were unable to perform the task with letter optotypes, a 3 m crowded Kay Picture Test book was used (Kay Pictures, Tring, Hertfordshire) and results were again recorded in LogMAR notation.

One drop of Proxymetacaine (0.5%) and Cyclopentolate (1%) (Minims, Chauvin Pharmaceuticals) were administered to participants, and a period of at least 30 minutes was left before measurement. A Royal Air Force (RAF) Rule (Richmond Products, Albuquerque, NM) was also used to check that the participants' accommodative amplitude had reduced to below two dioptres before proceeding to collect refraction data.

The extent of the visual field was assessed in participants with retinopathy using monocular Goldmann perimetry using a V4e target. The Goldmann perimeter has been shown to be the measure of choice for changes in peripheral vision and test-retest variability can be as low as < 20% (Bittner *et al.*, 2011). The target was brought from non-seeing to seeing along a minimum of six meridians, including the superior, inferior, nasal and temporal directions. The tested points were mapped and connected with straight lines to form isopters.

Central and peripheral cycloplegic autorefraction were measured with an open-field objective autorefractor (Shin-Nippon NVision-K 5001, Shin-Nippon, Japan), with a bespoke custom addition to allow for the collection of peripheral data. Participants were asked to fixate on a Maltese cross target at a distance of 20cm through a + 5.00 D Badal lens system and the mean of five readings were taken for each subject (see Section 2.6.1 for further details on autorefraction methodology and the Badal system used). AXL was measured using the IOLMaster 500 (Carl Zeiss, Jena, GmbH). Again, the average was taken from a minimum of five readings. Fundus photographs were taken with the

Topcon TRC-NW8 fundus camera (Topcon Corporation, Tokyo, Japan). For further information on the instrumentation used in this study see Chapter 2.

A debrief, and an opportunity for the participant to ask any further questions was given at the end of their involvement in the study. If the investigator had any concerns about the participant's vision or eye health, their parent / guardian was informed directly and appropriate referral/management was made. Following data collection, referrals were made to Birmingham Children's Hospital for two control group child participants without retinal pathology for the further investigation of their rapidly progressing high myopia.

6.4 Results

Four participants with retinal pathology participated in this study. Due to the small sample size, these are discussed in a case study style and age and or refraction is matched to other participants where appropriate. Depending on their age at time of participation, data for each participant were compared with normative data from either the six - seven or the 12 – 13 year old children studied in Chapter 4 of this thesis. This methodology was used to ensure that comparisons were drawn with a group which was as closely age matched with each individual participant as possible. All peripheral refraction data are presented graphically on a ten dioptre scale.

6.4.1 Participant A

Participant A is a female of Pakistani ethnic origin with Autosomal Recessive CSNB, who was eight years old at the time of participation in this study. Participant A was diagnosed with CSNB at one year old. Participant A has a positive family history of the condition, with her older teenage Sister and Mother both affected by the condition too. There is also a history of myopia in the family with both parents being moderately short-sighted.

On examination, distance LogMAR VAs were RE + 0.40 and LE + 0.36. A right alternating Esotropia was present at distance and near (Distance = 10 Δ base out, Near = 50 Δ base out) along with a fine horizontal jerk nystagmus. Visual fields are depicted in Figure 5.4.

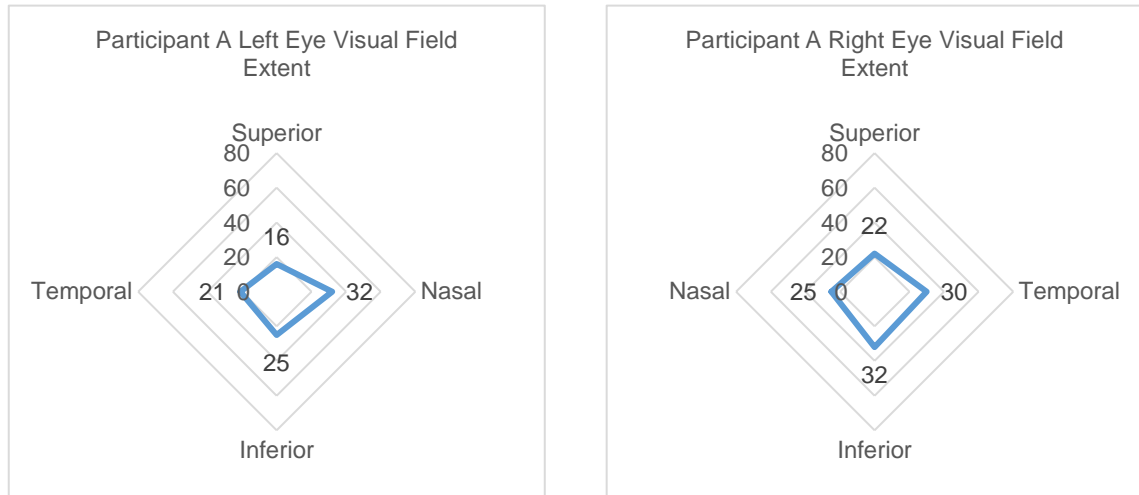


Figure 6.4 Goldmann perimetry plots of left and right eyes for participant A. Degrees from fixation are displayed on a scale extending vertically from the centre of each plot.

Participant A had no general health conditions, and IOP was normal on examination (15 mmHg bilaterally). Central refraction was found to be:

RE: - 13.68 / - 2.42 x 177, LE: - 13.20 / - 2.39 x 21

For peripheral refraction plots see Figure 5.5. AXL was RE: 26.80 mm LE: 26.54 mm.

See Figure 5.6.

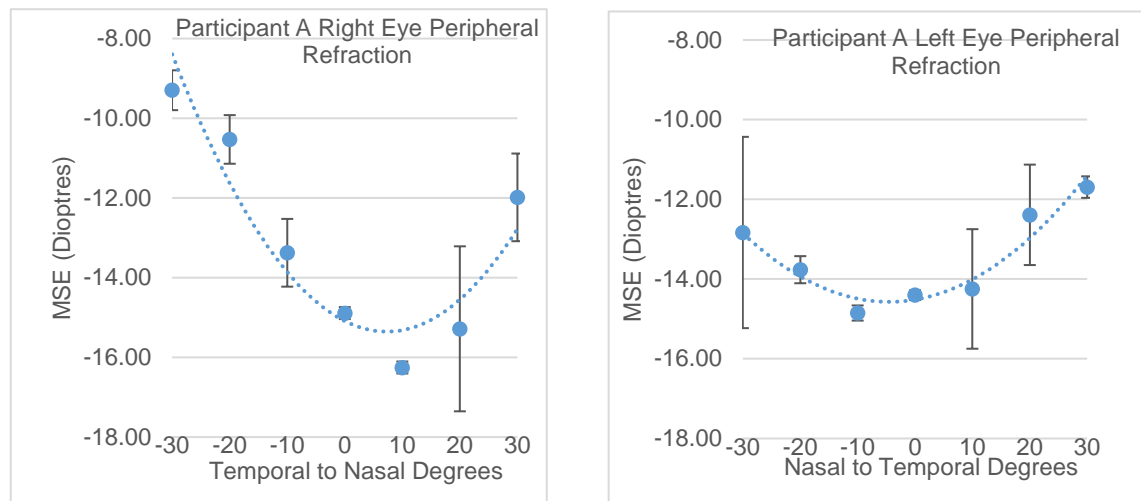


Figure 6.5 Plot of right and left eye peripheral refraction for participant A. Standard deviation error bars surround each point. Eccentricities from fixation are depicted on the x-axis.

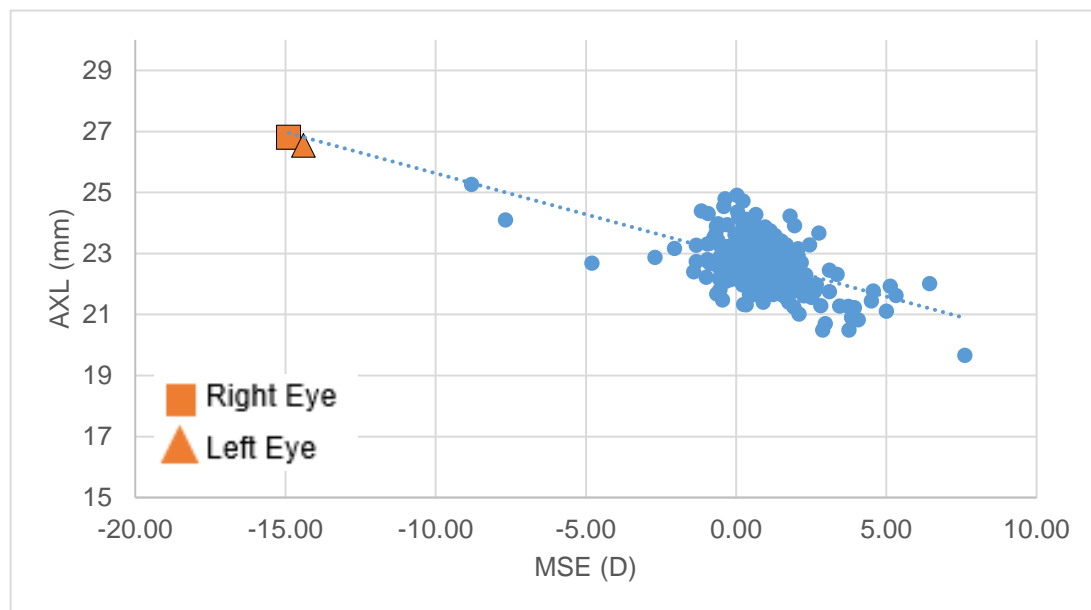


Figure 6.6 AXL for participant A (orange markers) plotted against normative data from aged 12 - 13 participants (blue markers).

Measurement of anterior chamber depth was not possible for this participant but WTR corneal astigmatism (see Section 5.3.2 for definition) was found in both eyes with keratometry readings of:

RE: 7.32 x 168, 7.00 x 78 and LE: 7.34 x 175, 7.09 x 85.

6.4.2 Participant B

Participant B is a female of South Asian ethnic origin with CSNB, who was 15 years old at the time of participation in this study. Participant B was diagnosed with Autosomal recessive CSNB and is registered as Severely Sight Impaired (SSI). There is a positive history of the condition on the maternal side of her family, with her Mother having the condition from childhood too.

On examination, distance LogMAR VAs were RE + 0.45 and LE + 0.52. Participant A had a manifest latent nystagmus and an intermittent alternating Exotropia. Visual fields were found to be restricted by Goldmann Bowl perimetry (see Figure 6.7).

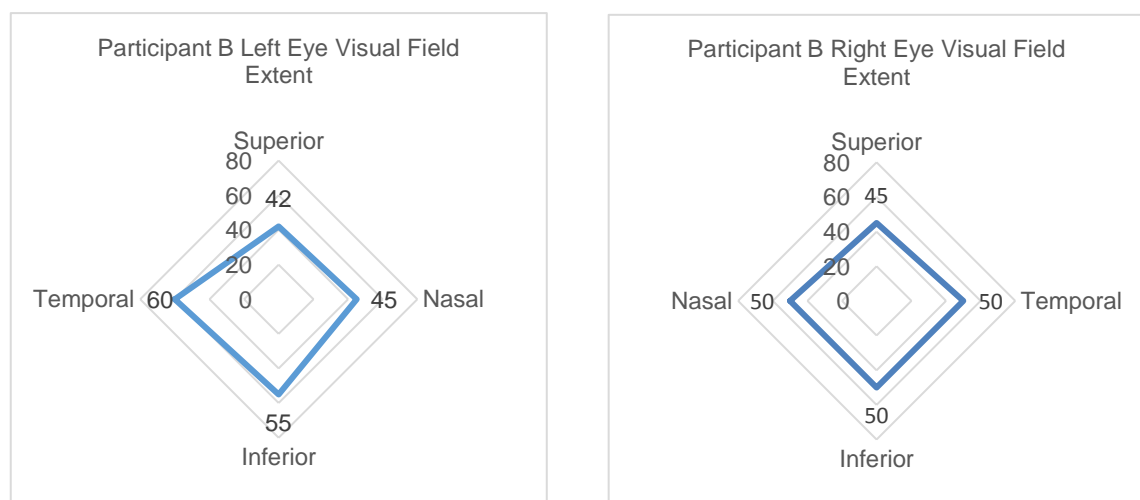


Figure 6.7 Goldmann perimetry plots of left and right eyes for participant A.

Participant B is being treated by her family doctor for migraines and alopecia, but no other general health problems were present. IOP was normal on examination. Central refraction was found to be:

RE: - 6.76 / - 1.54 x 118, LE: - 4.06 / - 1.50 x 66.

For peripheral refraction values see Figure 5.8. AXL was RE: 24.72 mm LE: 24.32 mm (see Figure 6.9). Anterior chamber depth was measured as 3.76 mm in the right eye and 3.68 mm in the left eye.

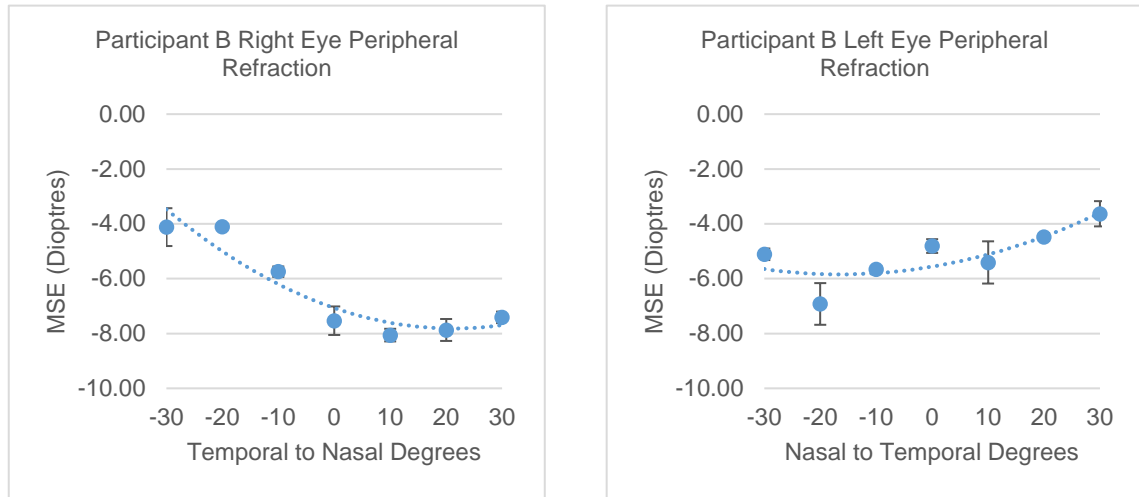


Figure 6.8 Plot of right and left eye peripheral refraction for participant B. Standard deviation error bars surround each point. Eccentricities from fixation are depicted on the x-axis.

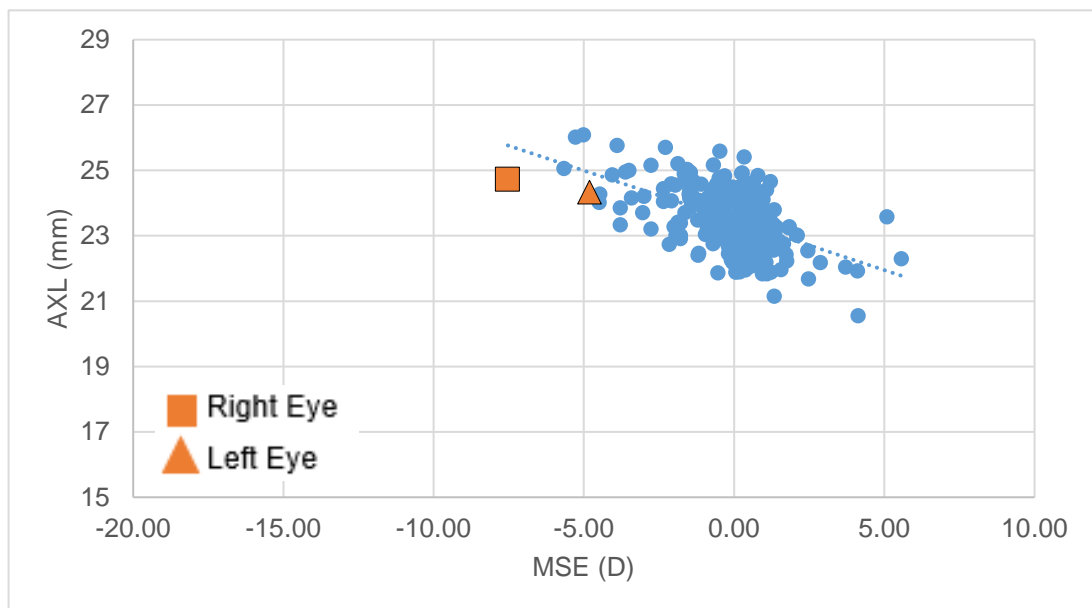


Figure 6.9 AXL for participant B (orange markers) plotted against normative data from aged 12 - 13 participants.

WTR corneal astigmatism was found in the right eye and OBL astigmatism in the left eye. Keratometry readings were:

RE: 7.45 x 169, 7.36 x 79 and LE: 7.49 x 35 and 7.30 x 125.

6.4.3 Participant C

Participant C is a female of South Asian ethnic origin with Autosomal Recessive bilateral progressive rod/cone dystrophy (type: RP), who was 11 years old at the time of participation in this study. Participant C was diagnosed with RP at eight years old and has a strong family history of the condition on the maternal side of her family with her cousins and grandma affected by the condition. It should be noted that participants C and D are siblings. Her older brother (participant D, see Section 6.4.4) has also been diagnosed with RP.

On examination, distance monocular LogMAR VAs were + 0.5 in each eye. There was a moderate right exotropia observable on dissociation, which recovered following blink. Visual fields were found to be severely restricted by Goldmann Bowl perimetry (see Figure 6.10).

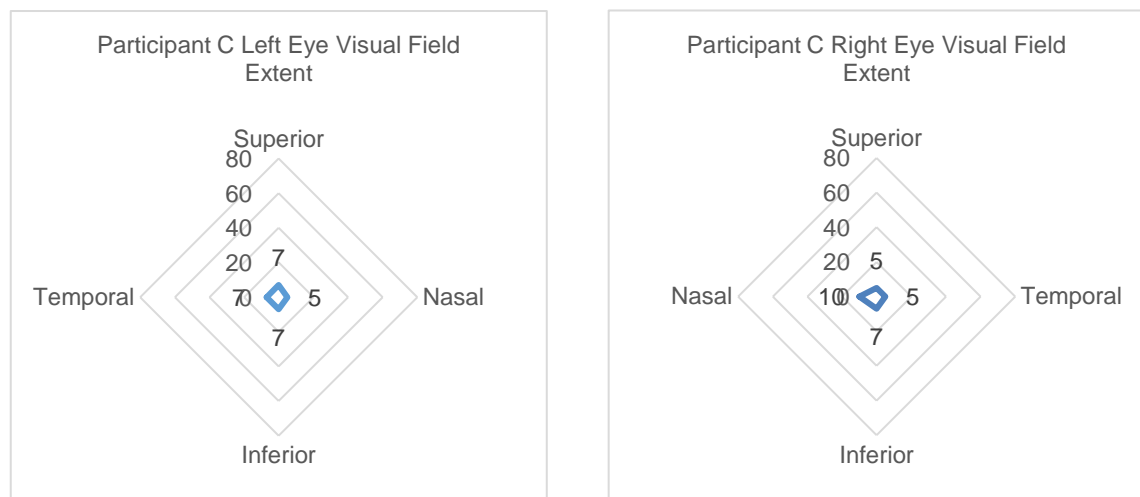


Figure 6.10 Goldmann perimetry plots of left and right eyes for participant C.

Mild mid-peripheral pigmentation outside of the vessel arcades was observable. Participant C had no general health or other ocular condition, and IOP was normal on examination (17mmHg bilaterally). Central cycloplegic autorefractometry was found to be:

RE: + 3.29 / - 1.86 x 10, LE: + 3.10 / - 2.28 x 179.

For peripheral refraction, plots see Figure 6.11. AXL was RE: 21.50 mm LE: 21.41 mm (see Figure 6.12). Anterior chamber depth was found to be 3.47 mm in the right eye and 3.39 mm in the left.

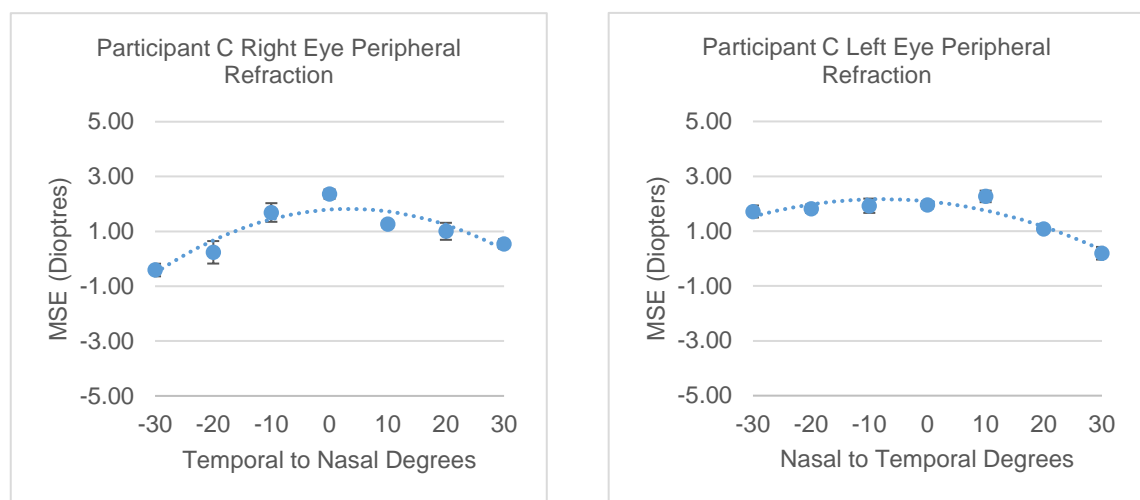


Figure 6.11 Plot of right and left eyes for participant C. Standard deviation error bars surround each point. Eccentricities from fixation are depicted on the x-axis.

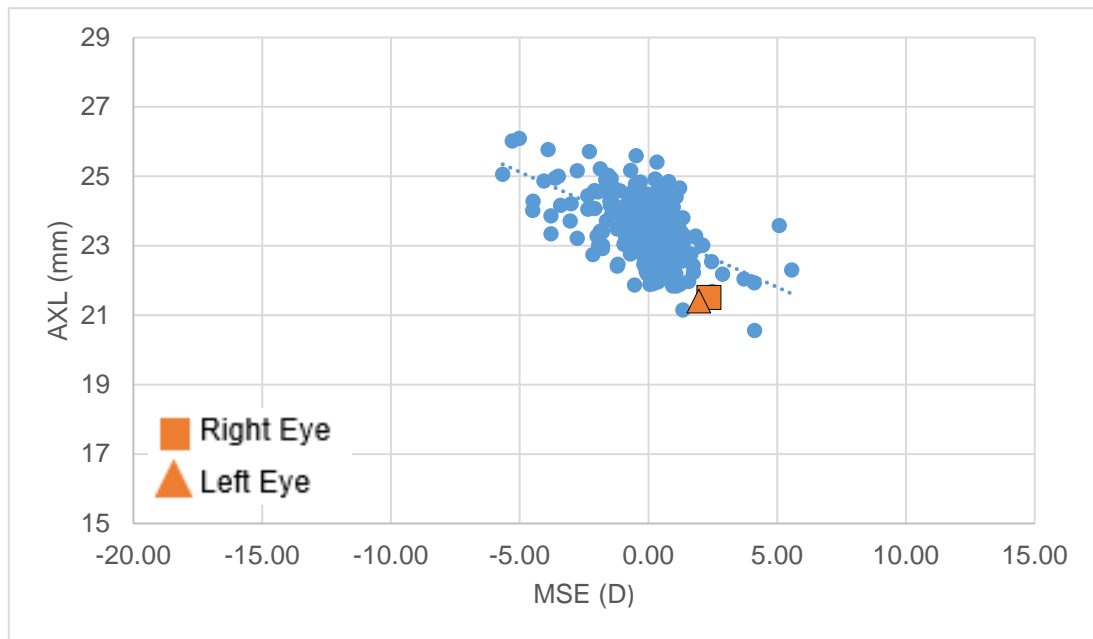


Figure 6.12 AXL participant C (orange markers) plotted against normative data from aged 12 - 13 participants.

There was WTR corneal astigmatism in both eyes. Keratometry results were:

RE: 7.49 x 2, 7.14 x 92 and LE: 7.52 x 173, 7.18 x 83.

6.4.4 Participant D

Participant D is a male of South Asian ethnic origin with RP, who was 14 years old at the time of participation in this study. Participant D was diagnosed with Autosomal Recessive Bilateral Progressive Rod/Cone Dystrophy (type: Retinitis Pigmentosa) at eight years old and has a strong family history of the condition on the maternal side of his family with his cousins and grandma affected by the condition. It should be noted that participants C and D are siblings. Participant D's younger sister (participant C, see Section 6.4.3) was diagnosed with RP after him.

On examination, distance LogMAR VAs was + 1.00 in the right eye and + 0.92 in the left. Visual fields were found to be severely restricted by Goldmann Bowl perimetry (see Figure 6.13).

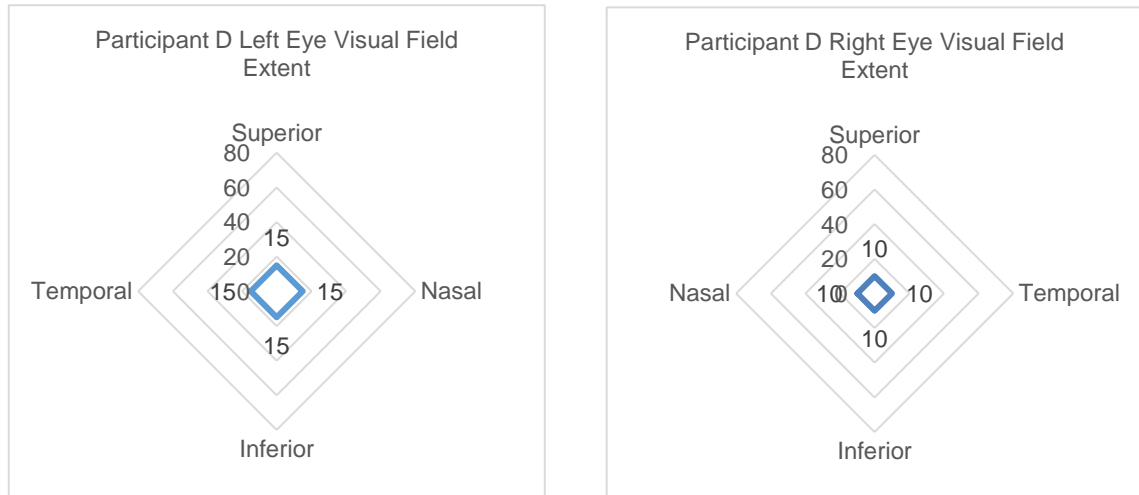


Figure 6.13 Goldmann perimetry plots of left and right eyes for participant D.

A 30^Δ left constant exotropia was present as well as horizontal nystagmus. Mild mid-peripheral pigmentation outside of the vessel arcades was observable. Participant D has asthma, but no other general health or other ocular condition, and IOP was normal on examination (15 mmHg bilaterally). Central refraction was found to be:

RE: - 0.38 / - 2.94 x 1, LE: - 0.13 / - 3.29 x 180.

Due to high the high amplitude of the nystagmus, it was only possible to measure peripheral refraction at 30 degrees nasal and temporal to the macula for each eye (see Figure 6.14).

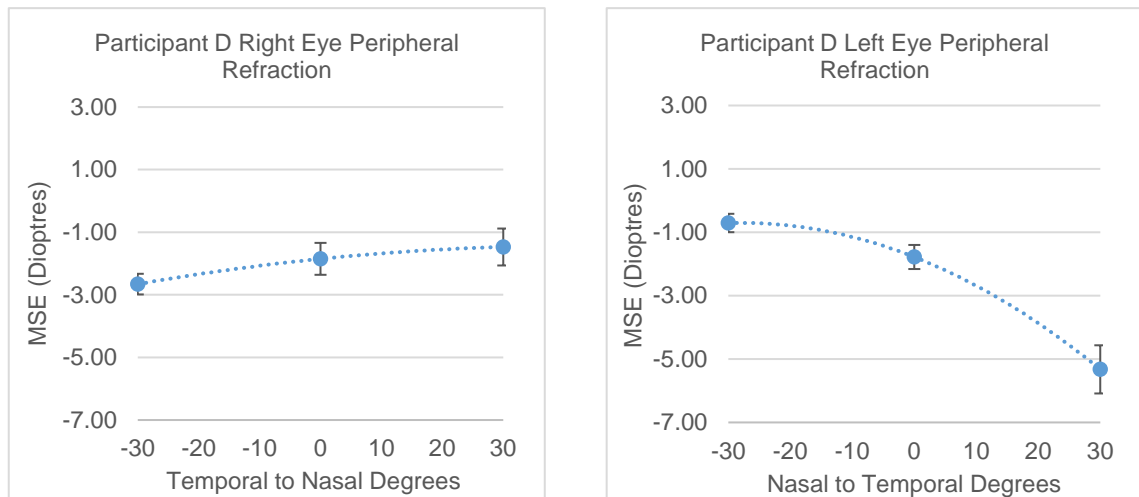


Figure 6.14 Plot of right eye for participant D. Standard deviation error bars surround each point. Eccentricities from fixation are depicted on the x-axis.

AXL was RE: 23.58 mm LE: 23.52 mm (see Figure 6.15). Measurement of anterior chamber depth was not possible for this participant. Both eyes exhibited WTR corneal astigmatism. Corneal curvature was:

RE: 7.89 x 4, 7.40 x 94 and LE: 7.97 x 180, 7.35 x 90.

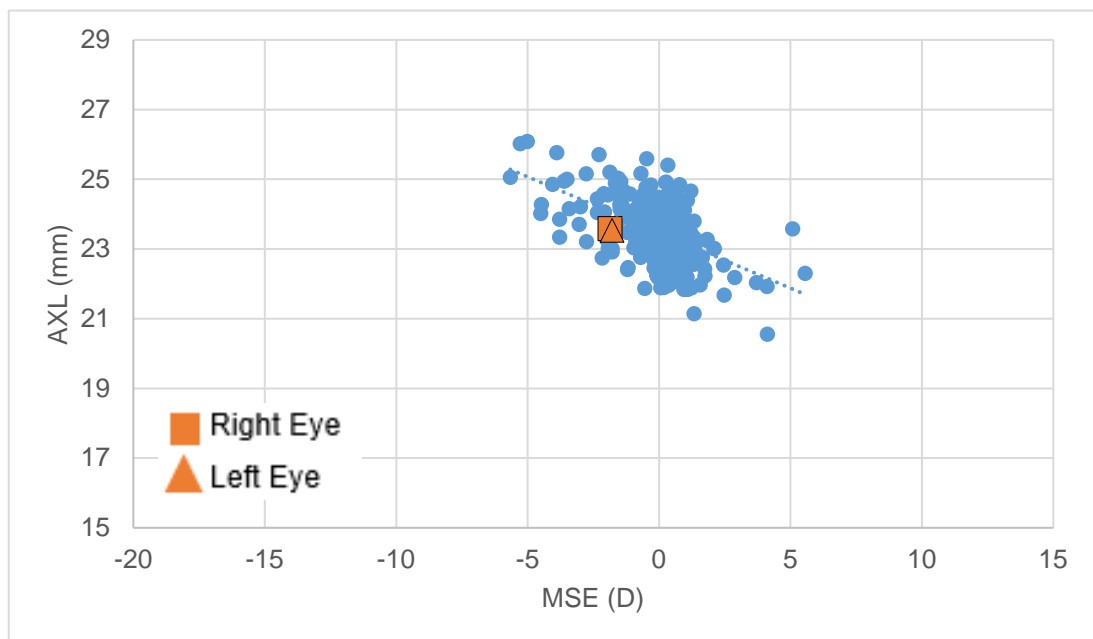


Figure 6.15 AXL for participant D (orange markers) plotted against normative data from aged 12 - 13 participants.

6.5 Discussion

This Chapter describes a cross-sectional study to elucidate the feasibility of collecting peripheral refraction, axial length and perimetry data in children aged five to 15 years with peripheral retinal pathology. The data collected was also analysed to determine if there are any obvious, striking differences between data in these cases compared to the normative data collected from children already described in Chapters 4 and 5 of this thesis.

Due to a small sample size, the data in this chapter are presented as a series of case studies. Owing to the nature of this format, there is no statistical testing possible to truly determine the nature of the relationship between AXL and refractive error in participants with CSNB and RP. Instead, here we are looking merely at the position of each participant's individual data relative to a normative sample of suitably age-matched children without ocular pathology. Consequently, comment is limited, except to say that the data from all four participants (A - D) appear grossly normal with regards to their position relative to the normative data and the line of best fit. It is clear that the myopic participants (A,B, and D) all have myopia which is accompanied by an increase in AXL. For all participants refractive error appears largely axial in nature rather than due to corneal or crystalline lens changes. The fact that the axial length of these eyes is in line with normal axial growth suggests that RP and CSNB are likely to be useful models to compare with normally developing eyes. However, it should be noted that for all eight eyes with pathology their data point sits slightly below the line of best fit. If there is a difference in the correlation between AXL and MSE in cases of peripheral retinal pathology such as RP or CSNB, it is only very slight and could only be elucidated with proper statistical testing with an appropriately large sample size.

To compare the difference in MSE between central and peripheral refraction, the central MSE was subtracted from the values for the 30 degree eccentricities (Mutti *et al.*, 2000). The peripheral differences, from primary gaze refraction, for the nasal and temporal retina, for children with pathology are presented in Table 6.1.

Case Study	RIGHT EYE			LEFT EYE		
	MSE (D)	T	N	MSE (D)	N	T
A	-14.89	H +5.59	H +2.89	-14.40	H +1.41	H +2.60
B	-7.53	H +3.41	H +0.12	-4.81	M -0.30	H +1.18
C	+2.36	M -1.95	M -1.82	+1.96	M -0.25	M -1.77
D	-1.85	M -0.81	H +0.38	-1.76	H +1.76	M -3.56

Table 6.1 Peripheral refraction differences, from primary gaze refraction (MSE), for the nasal and temporal retina, for case studies A - D. H denotes a hyperopic relative peripheral refraction, while M denotes a myopic relative refraction.

The peripheral refraction findings are largely typical of peripheral refraction patterns reported in previous studies of children and young adults without ocular disease. These studies have found that emmetropic and hyperopic groups tend to have relative peripheral myopia (Atchison *et al.*, 2005b; Millodot., 1981; Mutti *et al.*, 2000; Sng *et al.*, 2011a). Myopic eyes however, have been shown to exhibit relative peripheral hyperopia in the nasal and temporal fields compared to primary gaze (Atchison *et al.*, 2006; Berntsen *et al.*, 2010; Chen *et al.*, 2010; Kang *et al.*, 2010; Millodot, 1981; Mutti *et al.*, 2000; Radhakrishnan *et al.*, 2013; Sng *et al.*, 2011a; Yamaguchi *et al.*, 2013). For both participants (A and B) who had relative peripheral hyperopia nasally and temporally, the temporal retinal field was more hyperopic than the nasal retinal field. This is consistent with the findings of Berntsen and Kramer (2013) Lin *et al.*, (2010) and Sankaridurg *et al.*, (2011). The most marked peripheral hyperopia was for participant A, who was vastly more myopic. This is supported by the work of Atchison *et al.* (2006) who found that to

some extent, the degree of relative peripheral hyperopia increases according to the degree of myopic central ametropia.

The normal visual field extent in healthy eyes is approximately 100° temporally, 75° inferiorly and 60° nasally and superiorly (Spector, 1990). For the children with RP and CSNB in this study, visual fields were comparatively restricted, between ten and 60 degrees for all meridians. For breakdown by meridian see Table 6.2.

Range of field restriction (degrees)	
Superior	5 to 45
Inferior	7 to 50
Nasal	5 to 50
Temporal	5 to 60

Table 6.2 Breakdown of visual field restriction for participants with retinal pathology by visual field meridian.

It is known that a gradual loss of rod and cone photoreceptors is responsible for advancing tunnel vision in RP (Hamel, 2006). Both participants with RP in this study showed a restriction of visual field extent between 5 and 15 degrees. Both participants with CSNB had slightly larger isopters, between 16 and 50 degrees. These findings are not wildly dissimilar from the iatrogenic peripheral visual field deprivations induced in Smith *et al.*'s 2005 study, where diffusers with a 24° or 37° central opening were used to deprive the periphery of form vision. As with all studies of human disease, there is a range of severity and difference in progression course between individuals, so it is not possible to match the visual field restriction criteria for animal models exactly. Nevertheless, visual field statuses in RP and CSNB appear to be within a range to provide useful models for comparison with animal work in this respect. However, much larger numbers of participants, at least matching the original sample size calculation (see Appendix 10.8) would be needed to allow proper statistical analysis to be performed, and

to evaluate any correlations accurately. Participants should be further grouped into categories by severity of visual field restriction to allow for deeper analysis. A future study would also benefit from being longitudinal, to assess the effect of pathological peripheral damage on ocular development over time. Using RP and CSNB for this work would be of interest to compare the effect on refractive and biometric status of one progressive and one stationary retinal condition.

Refractive and corneal astigmatism data were collected from all participants. All participants (A – D) had refractive astigmatism over 1.00 DC in both eyes. As a point of comparison, in the study described in Chapter 5 of this thesis, the proportions of six to seven year old and 12 to 13 year old children with refractive astigmatism ≥ 1.00 DC were 12.1% and 12.3% respectively. In the current study, three eyes had OBL refractive astigmatism, while the remaining five had WTR astigmatism. This is analogous to the findings of Chapter 5, where the majority of child participants had OBL astigmatism, however the majority of cases over 2.00 DC were WTR. Corneal astigmatism was also comparable with Chapter 5, with the most common corneal astigmatism condition being WTR (seven out of eight eyes). Seven out of eight eyes in the current study had corneal astigmatism ≥ 1.00 DC compared to 33.6% in the six to seven year olds, and 29.4% in the 12 to 13 year olds. Though no conclusions can be drawn about the state of astigmatism in RP and CSNB due to this study not being powered for statistical significance, the findings of this study mean it seems reasonable to suggest that there may be a high prevalence of astigmatism in these conditions, though the distributions of axes as WTR, ATR or OBL may be comparable to those found in a population without eye disease.

In future work, ERG would be a useful tool, particularly in the cases of CSNB, to determine which photoreceptors are affected. Although both participants in this study

had Autosomal Recessive CSNB, it was not determined whether this was the complete or incomplete form. The incomplete type is characterised by both a reduced rod b-wave and substantially reduced cone response on ERG. The complete type is associated with a drastically reduced rod b-wave response but largely normal cone b-wave amplitude (Audo *et al.*, 2009). Knowing whether both the rods and cones or just the rod cells are affected would give further insight into which retinal elements are important in emmetropisation. Furthermore, retinal OCT may be informative as to the integrity of the retina in participants with RP and CSNB.

Depending on their age at time of participation, data for participants A - D were compared with normative data from either the six - seven or the 12 - 13-year-old children studied in Chapter 4 of this thesis. This methodology was used to ensure that comparisons were drawn with a group which was as closely age matched with each individual participant as possible, as it is clear from Chapter 4 of this thesis that the relationship between refractive error and AXL is different for differently aged populations. A limitation of this approach was that there was a maximum difference between participant and control matched group of up to 2 years in age (participant D). However, it would not have been possible to match participants with an appropriate individual control participant matched for age, gender and ethnicity due to limited recruitment. Future work should ensure closer age matching for improved accuracy. This could be achieved by extending a study of normative data on the correlation between MSE and AXL, such as that previously described in Chapter 4 of this thesis to include further age groups.

In summary, this study suggests that RP and CSNB in children may be appropriate models for the investigation of the influence of the retinal periphery on emmetropisation in humans, however the validity of this research design would have to be confirmed by a study with an adequately large sample size. Having a large-scale longitudinal study

would elucidate further if the findings from animal studies can be applied to humans. Though recruitment was limited, this study has shown that this nature of data collection in participants with RP and CSNB aged between five and 15 years is feasible.

7. A FEASIBILITY STUDY ON THE INFLUENCE OF AXIAL LENGTH AND REFRACTIVE ERROR ON CENTRAL AND PERIPHERAL RETINAL LIGHT SENSITIVITY

7.1 Introduction

It is well documented that many factors influence retinal sensitivity to light, with increasing age (Brenton and Phelps, 1986, Haas *et al.*, 1986), certain pathologies and certain medications (Zulauf *et al.*, 1986) all known to adversely affect responses. However, whether a correlation exists between AXL and visual field sensitivity remains undetermined and is relevant to understanding the structural variations that occur in ametropia.

The majority of myopia is axial in nature with the principal correlate being an increase in vitreous chamber depth (Bullimore *et al.*, 1992; Logan *et al.*, 2005; Strang *et al.*, 1998), and it is widely accepted that myopic eyes are generally larger in size than emmetropic or hyperopic eyes (Atchison *et al.*, 2004; Atchison *et al.*, 2005a; Logan *et al.*, 2005; Gilmartin, 2004; Gilmartin *et al.*, 2013; Singh *et al.*, 2006). Evidence suggests that in these cases the normal retina is subject to stretch and accounts for the increased posterior globe size (Bradley *et al.*, 1983; van Alphen, 1961). The retinal photoreceptor mosaic is the primary sampling matrix of the human visual system (Ahnelt, 1998), and its topography serves as a limit to resolution. It seems reasonable to suggest that in these cases, physical stretching of the retina may lead to changes in the maximum resolvable spatial frequency due to decreased retinal sampling density. The eccentricity at which this is measurable is currently unknown.

Approximately 4.6 million cones and 92 million rod photoreceptors are packed in a non-uniform distribution within the neurosensory retina (Curcio *et al.*, 1990). The cone

photoreceptors are most highly concentrated at the fovea (approximately 199,000 cones/mm²), and their density decreases with increasing eccentricity from the central retina (Curcio *et al.*, 1990). There are minimal rods within the fovea and an area of approximately 0.35mm² around the fovea in which is completely absent of rod cells (Curcio *et al.*, 1990). Peak rod density occurs in an elliptical ring-shaped zone approximately 3 - 5 mm from the foveola (Curcio *et al.*, 1990; Jonas *et al.*, 1992). Furthermore, differences in cone density between retinal quadrants have been identified. A higher density of cones has been found in the inferior mid-peripheral retina compared to the superior mid-periphery (Curcio *et al.*, 1990). Cone density in the nasal retina has also been shown to be 40-45% greater than at an equivalent degree from the fovea in the temporal meridian (Curcio *et al.*, 1990).

The mechanism of morphologic change in myopia development is currently unknown, but various models have been proposed. Identification of the mechanism by which elongation occurs is crucial to understanding why there is potential for differences in visual field sensitivity to occur with varying levels of ametropia. Modern models of myopic growth propose that globe expansion does not occur regularly, and that stretch is not limited to the pre-retinal aspect of the globe. However, there is not as yet one model that receives universal agreement, and the consensus view is a combination of the existing models (Verkicharla *et al.*, 2012).

Strang *et al.* (1998) proposed three potential models for the nature of growth in axial myopia: equatorial stretch, global expansion, and posterior pole stretch. More recently, a fourth model has been suggested: axial expansion (Verkicharla *et al.*, 2012) (see Figure 7.1). In the equatorial stretching model, the axial stretch is confined to the equatorial region of the globe. Should this be the sole mechanism for axial elongation, no anatomical changes or change in sampling density should be observable at the

posterior pole. With global expansion, vitreous chamber growth is achieved by uniform expansion across the entirety of the sphere, whereas, in the posterior pole model, stretch occurs radially and is confined to the posterior pole (Strang *et al.*, 1998; Verkicharla *et al.*, 2012). The axial expansion model is a combination of the equatorial and posterior pole expansion models (Verkicharla *et al.*, 2012). Unlike the other three models which result in a spherical surface, axial expansion would give a prolate ellipsoid surface (Verkicharla *et al.*, 2012). The global expansion, posterior polar and axial expansion stretch models would all theoretically lead to a decrease in photoreceptor cell density in eyes with axial myopia as the normal retina directly undergoes stretch to achieve the increased posterior ocular volume. Should this be the case, it is assumed that emmetropic and hyperopic eyes should show a relative increase in peripheral light sensitivity compared to myopic eyes.



Figure 7.1 Current models of retinal stretching in myopia: a) global b) equatorial c) posterior polar and d) axial expansion. The solid circles represent the shape of the retina of an emmetropic eye, the dashed shapes represent the myopic retinas, and the arrows indicate the regions of stretching. Reproduced with permission (Verkicharla *et al.*, 2012) [Eye shape and retinal shape, and their relation to peripheral refraction, Verkicharla, P. K., Mathur, A., Mallen, E. A., Pope, J. M. and Atchison D. A. Ophthalmic and Physiological Optics Vol. 32, Copyright © 2012 The College of Optometrists].

MRI has shown that the human eye is spherical in shape up until the posterior 25% where there are characteristic changes in conformation (Singh *et al.*, 2006). There is good evidence to support axial growth occurring non-uniformly (Logan *et al.*, 2004b). It is therefore expected that all retinal locations will not be affected equally in the ametropic

eye as there will be a disparity of stretch exerted across different retinal quadrants during ametropic expansion.

This Chapter will describe a feasibility study on the influence of axial length and refractive error on central and peripheral retinal light sensitivity. The research questions posed are: does retinal light sensitivity depend on AXL and refractive error, and can this tell us anything about the nature of retinal stretching in myopia? Particular reference will be made to which axial expansion model (Strang *et al.*, 1998; Verkicharla *et al.*, 2012) is most applicable to the nature of ocular expansion in myopia.

7.2 Methods

Since differential light sensitivity decreases as a function of age, to minimise this effect, young observers from Aston University's student population were recruited. 34 visually normal individuals (7 Males, 25 females) aged between 18 and 23 years (mean = 20 years, SD = 1.37) were subsequently enrolled in this study. A short ocular and general health history encompassing inclusion/exclusion criteria was taken prior to the measurement to ensure participant eligibility. Exclusion criteria were: iatrogenic change in refractive status, for example, previous refractive surgeries or surgically induced ametropia; astigmatism of greater than 1.00 DC in the test eye; personal or family history of systemic disease; use of medication known to affect the retina; retinal disease; media opacity and glaucoma.

Of the 34 subjects enlisted and screened, two were excluded from the study on account of having a corrected distance VA of less than 0.0 LogMAR and one excluded for having astigmatism of greater than 1.00 DC. The total number of participants whose data was analysed in this study is 31.

Right eye data were collected from each participant. Distance visual acuities were recorded in LogMAR notation using an illuminated 4 m ETDRS chart (Precision Vision, La Salle, IL, USA).

Non-cycloplegic distance autorefraction was measured with an open-field objective autorefractor (Shin-Nippon NVision K 5001, Shin-Nippon, Japan). Participants were asked to fixate on a Maltese cross target viewed through a Badal lens system set up to ensure zero accommodation, and the mean of five readings were taken for each subject. AXL was measured using the IOLMaster 500 (Carl Zeiss, Jena, GmbH). Again, the average was taken from a minimum of five readings.

The perimeter used for determining visual field sensitivity was a Humphrey Field Analyser 750 (Carl Zeiss, Jena, GmbH), generally considered to be the “gold standard” automated perimeter. The Humphrey Field Analyser 750 model has an integrated feature which allows the operator to programme their own visual field test by selecting the desired strategy and test locations (in graph coordinate form). Using this feature, a custom full threshold test that used a 4 - 2 dB double reversal staircase strategy was designed for use in this study (see Section 2.7). The number of stimulus locations was chosen in order to reduce testing time and therefore reduce the influence of the fatigue effect (see Figure 7.2), which is a documented confounding factor in perimetry and thought to derive from binocular rivalry, a cortical phenomenon (Blake, 1989; Blake and Overton, 1979). On this bespoke test, the measurement points were placed at 10-degree intervals along the horizontal and vertical midlines as well as along the diagonal meridians. For further information on the instrumentation used in this study see Chapter 2. Non-emmetropic participants were corrected prior to perimetry with their own distance vision contact lenses or in one case, a full aperture spectacle trial lens inserted into the lens-holder of the perimeter and placed as close to the lash plane as possible.

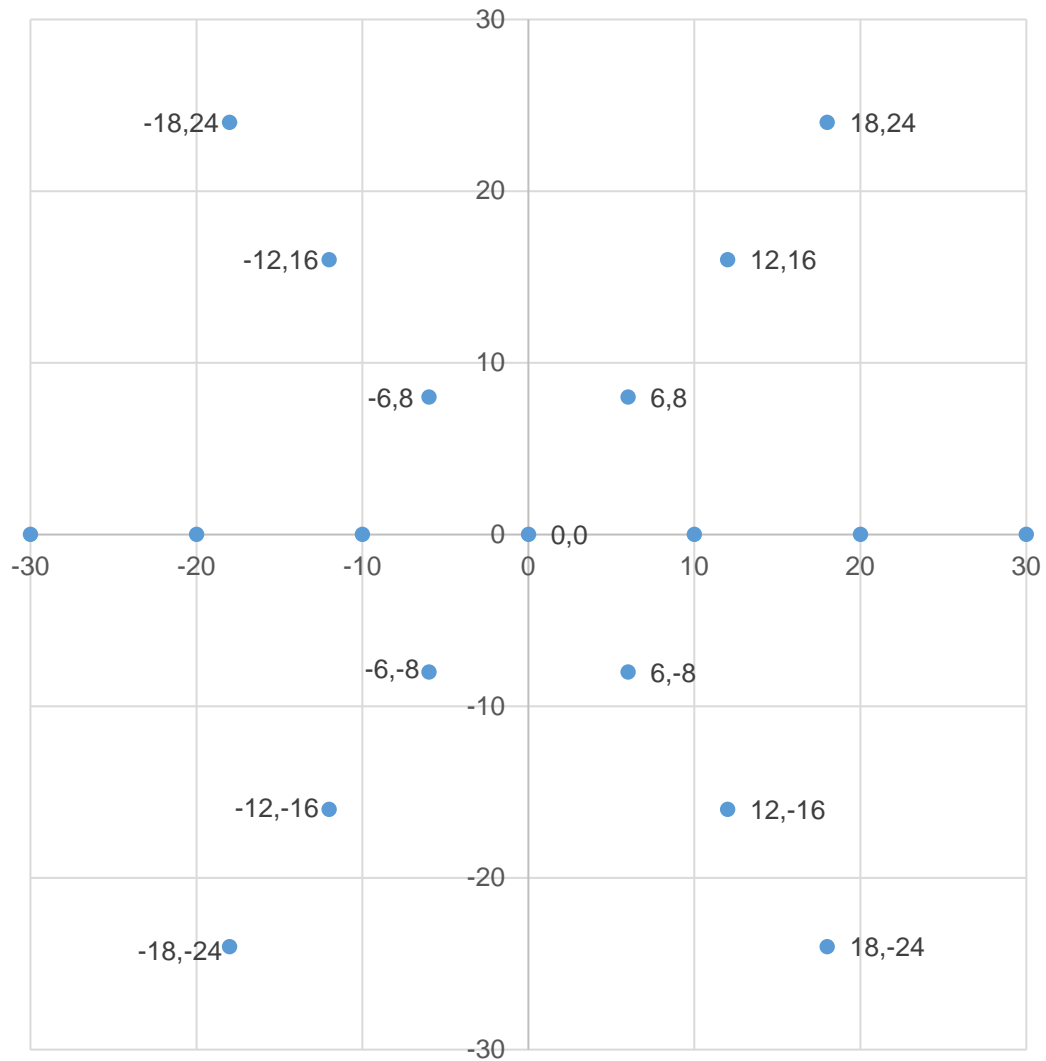


Figure 7.2 Graph showing the stimulus positions of the custom grid designed for the Humphrey 750 Field Analyser. Grid x-y coordinates (degrees) are shown below the data points and the degrees from fixation above each location. The foveal threshold (0,0) option was enabled.

Each subject was assessed on two different occasions. At the first visit, subjects underwent autorefraction and biometry measurements in addition to perimetry. At the second visit, between five to 14 days after the initial test, perimetry was repeated. Only the results from this second visual field test were analysed in this study to minimise the known influence of learning on the visual field outcome (Marra and Flammer, 1991).

7.2.1 Ethical considerations

Ethical approval was acquired from Aston University's Research Ethics Committee (see Section 10.1). The study conformed to the tenets of the Declaration of Helsinki. Written consent/assent was obtained from all participants prior to measurement. An opportunity was given to address any questions or concerns that the participant had at this stage and throughout the remainder of their participation in the study.

7.2.2 Sample size calculation

The following values were analysed by a linear bivariate regression one-sample t-test to calculate target sample size (G*Power 3 (Faul *et al.*, 2007)). α level was set at 5% and a β level at 0.5%. Based on previous studies, the average within-subject variability (short-term fluctuation (SF)) in healthy-eyed individuals is between 1 and 2 dB (Cubbridge *et al.*, 2002; Flammer *et al.*, 1985; Wild *et al.*, 1998). Using a SF value of 2 dB, a sample of 31 would give a 95% confidence level of detecting differences in visual field sensitivity.

7.3 Results

Mean Spherical Errors (MSE) were calculated for each participant. 11 subjects were non-myopic (MSE = > -0.50 D), and 20 were myopic (MSE = ≤ -0.50 D). Refractive error (MSE) ranged between + 1.85 D and - 6.75 D. The mean MSE was - 1.91 D (SD = 2.15). The mean AXL was found to be 24.17 mm (SD = 1.33).

The data were tested for normality using the Shapiro-Wilk statistical test. AXL and mean spherical error were both found to be normally distributed ($p = 0.89$ and $p = 0.21$ respectively). Preliminary analysis showed the relationship to be linear as assessed by visual inspection of a scatter plot, there were no outliers.

Pearson's correlation tests were run to determine the nature of the correlation between AXL and MSE. There was a strong negative correlation between MSE and AXL ($r(31) = -0.80$ $p < 0.005$), with MSE statistically explaining 65% of the variation in AXL (see Figure 7.3).

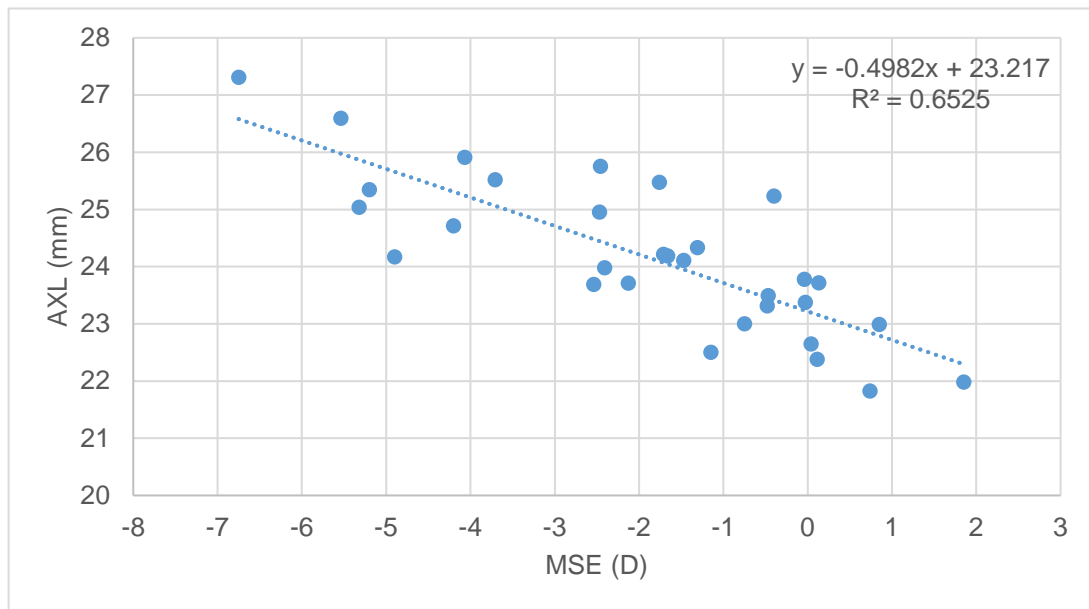


Figure 7.3 Correlation between AXL (mm) and MSE (Dioptres).

Light sensitivity (dB) at the foveal location (0,0) was analysed as a function of AXL. A Shapiro-Wilk test found that foveal light sensitivity was not normally distributed ($p = 0.02$).

The reciprocal of the gradient (m) derived from the equation of the line of best fit ($y = mx+c$) was calculated for the data presented in Figure 7.3 Correlation between AXL (mm) and MSE (Dioptres). This produces a value for the amount of change in light sensitivity per mm increase in AXL. There was a decrease in foveal light sensitivity to the degree of 1.43 dB per mm increase in AXL. However, Spearman rank - order correlation analysis showed no statistical significance ($r_s(29) = -0.31$ $p = 0.10$) (Figure 7.4).

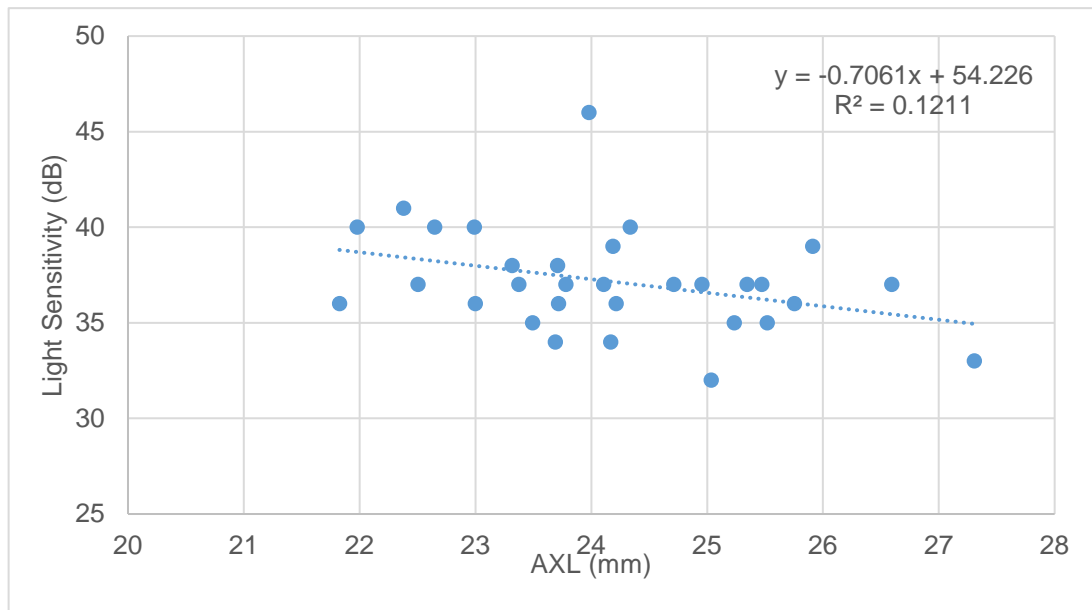


Figure 7.4 Correlation between foveal light sensitivity (dB) and AXL (mm).

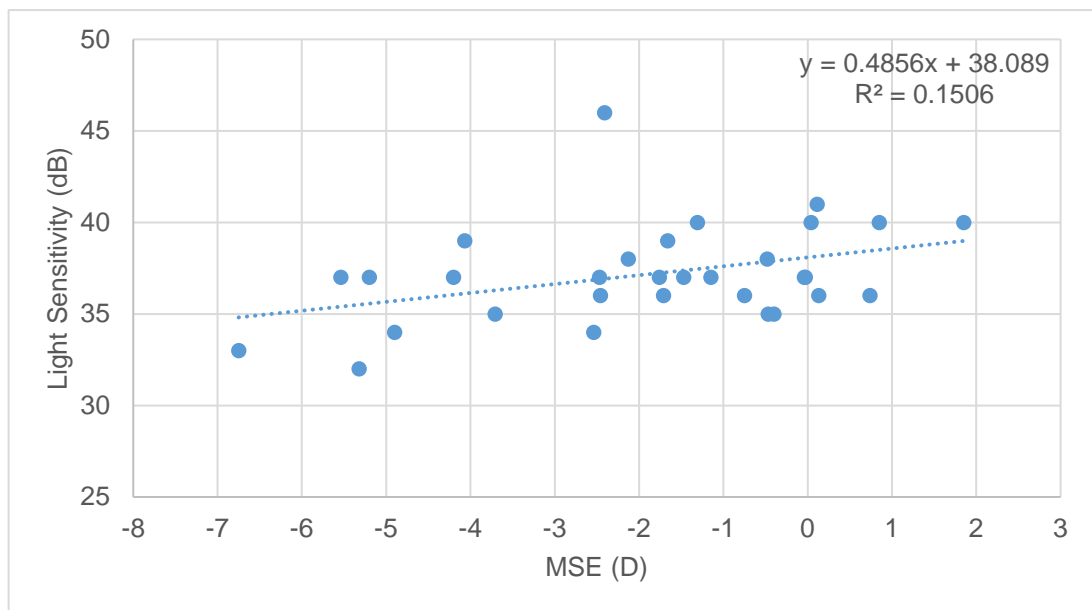


Figure 7.5 Correlation between foveal light sensitivity (dB) and mean spherical error (Dioptres).

However, a weak positive correlation was found between light sensitivity and MSE, with each 1.00 D increase in myopia corresponding to a 2.05 dB decrease in light sensitivity. This was significant ($r_s(29) 0.39$ $p = 0.03$) (Figure 7.5).

Furthermore, differential light sensitivity at each stimulus location was plotted as a function of both MSE (see Figure 7.6) and AXL (see Figure 7.8) and these were subjected to Spearman rank - order analysis. Apart from the foveal threshold described above, a statistically significant correlation was found at one location only in both the analysis of AXL and MSE. This point was at ten degrees from fixation along the horizontal midline of the temporal field (see Figures 7.7 and 7.9).

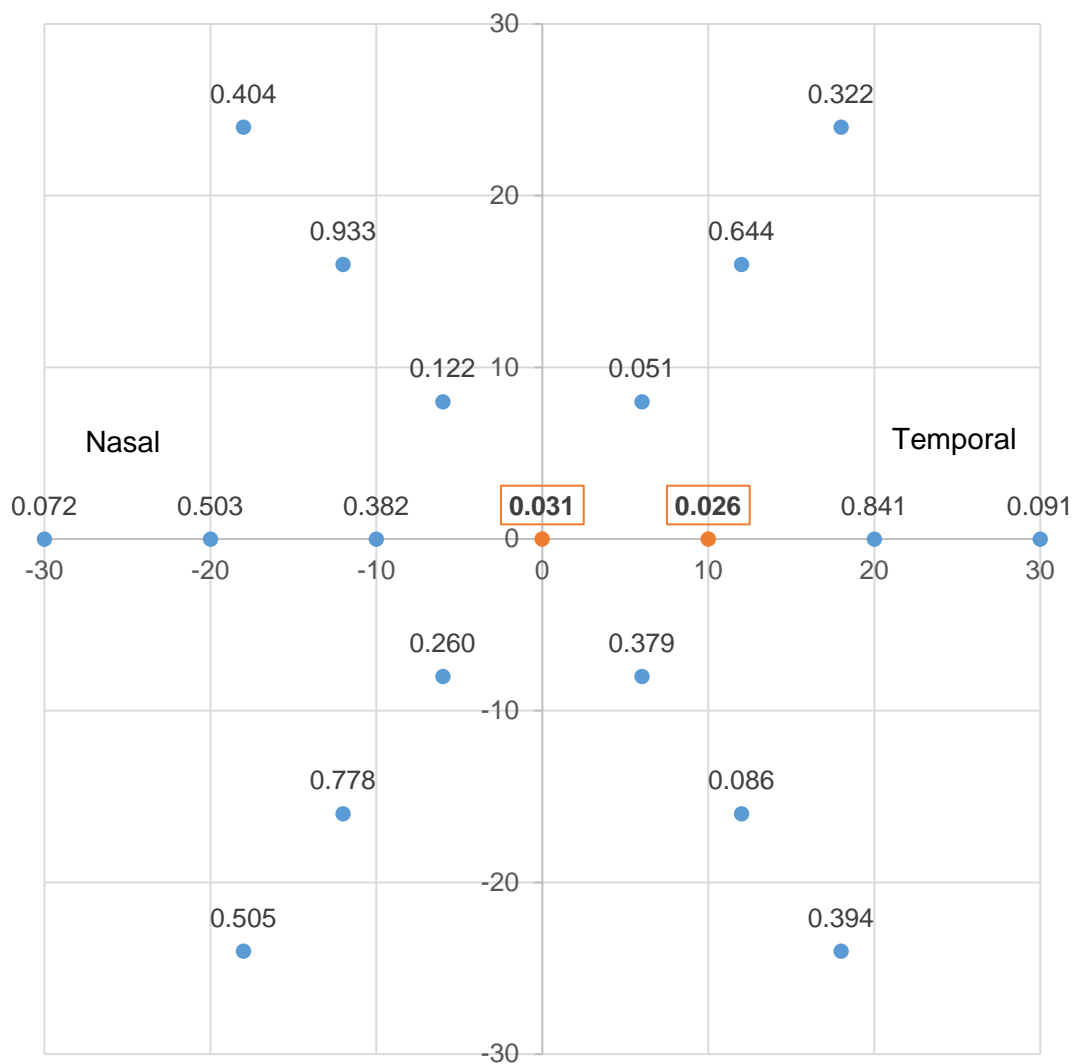


Figure 7.6 *p* values for the correlation between light sensitivity and MSE at each stimulus location, showing a significant value only at the fovea and at 10 degrees temporally on the horizontal axis of the visual field (both positions are marked in orange with a surrounding box).

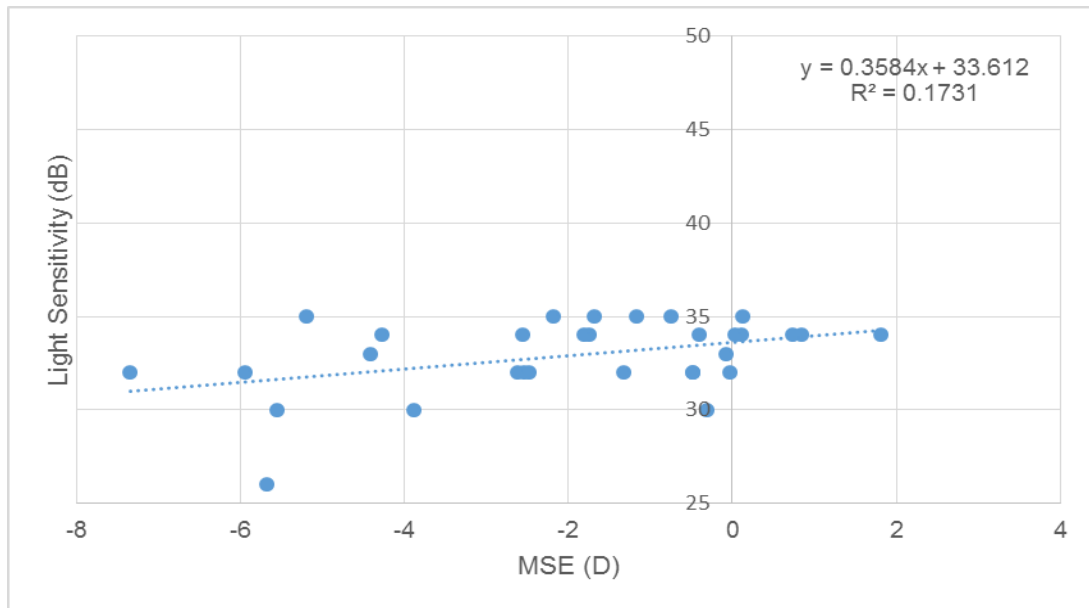


Figure 7.7 Correlation between MSE and light sensitivity for location (10, 0), where statistical significance was found.

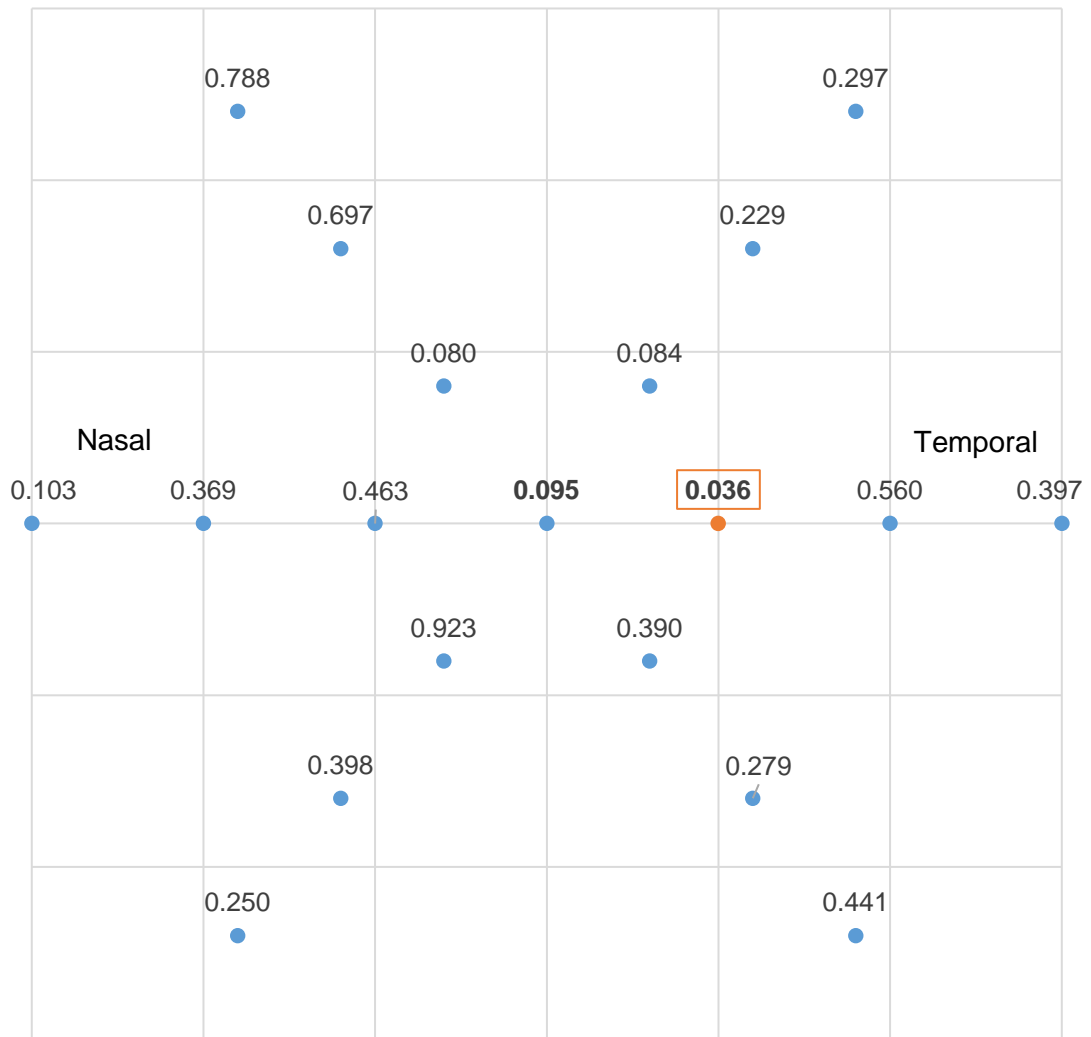


Figure 7.8 p values for the correlation between light sensitivity and AXL at each stimulus location, showing a significant value only at 10 degrees in the temporal visual field (marked with a surrounding box).

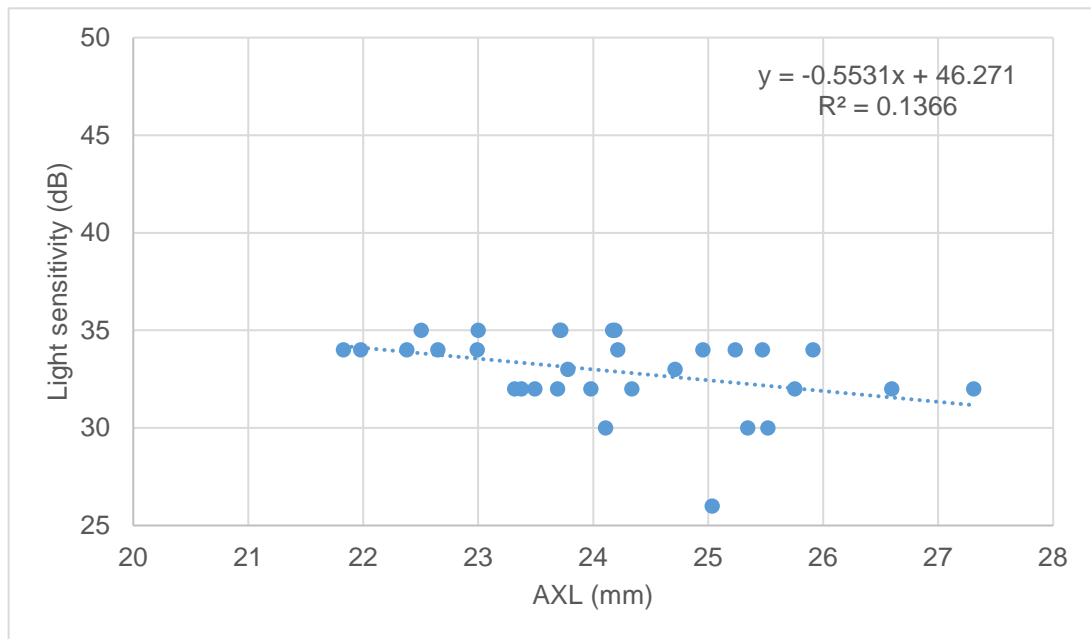


Figure 7.9 Correlation between AXL and Light sensitivity for location (10, 0), where statistical significance was found.

The difference in light sensitivity (dB) between the stimulus locations ten and 30 degrees from fixation were calculated for each diagonal quadrant as well as for the horizontal axis in order to quantify the drop - off in sensitivity for each individual participant. The mean drop off in sensitivity for each quadrant of the visual field were as follows: SN = - 4.65 dB (SD = 2.15), ST = - 4.55 dB (SD = 3.05), IN = - 4.23 dB (SD = 2.35), IT = - 2.94 dB (SD = 2.41).

Regression Slopes were plotted as a function of MSE and AXL separately for each quadrant (Figure 7.10). Spearman rank- order analysis found no significant correlation for reduction in the threshold for any quadrant of the visual field except in the inferior nasal quadrant for MSE but not AXL (Figure 7.11).

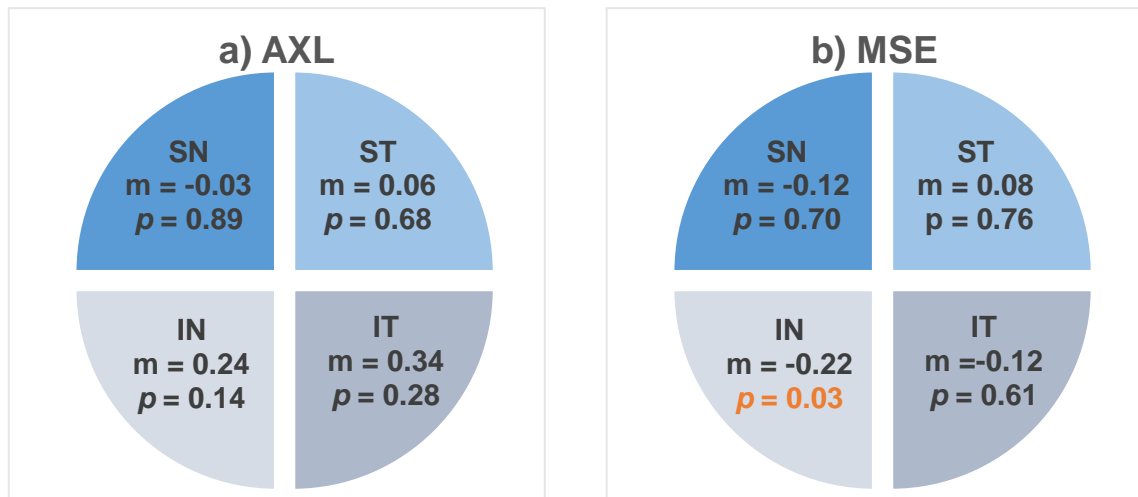


Figure 7.10 Slope gradients (m) and probability values (p) for 10 to 30 degree light sensitivity drop-off compared to a) AXL and b) MSE in each quadrant of the visual field (SN = Superior-Nasal, ST = Superior-Temporal, IT = Inferior-Temporal, IN = Inferior-Nasal).

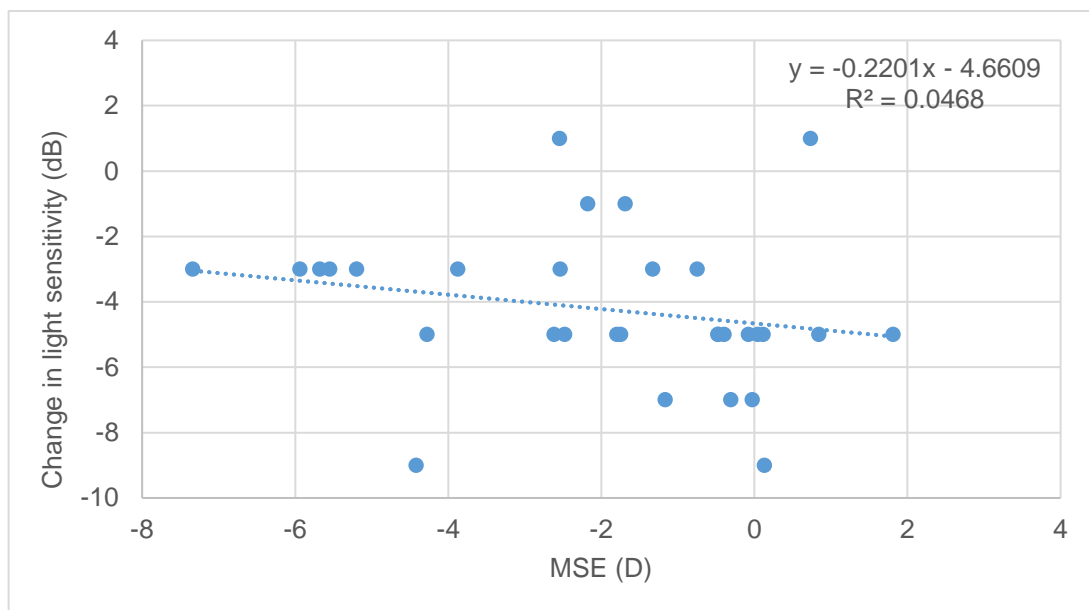


Figure 7.11 Change in light sensitivity (dB) between points 10 degrees and 30 degrees from fixation in the Inferior-Nasal visual field.

7.4 Discussion

This chapter describes the methodology and findings of a cross-sectional feasibility study on the effect of refractive error and ocular length on visual field functionality in a healthy population. It was predicted that variations in globe conformation which are characteristic

in myopia, as well as a reduced efficacy of the photoreceptor mosaic precipitated by this, would cause a reduction in visual field sensitivity in axially longer eyes.

A statistically significant correlation was found between foveal AXL and refractive error, which is concordant with previous work (Bullimore *et al.*, 1992; Chui *et al.*, 2008; Grosvenor and Scott, 1993; Strang *et al.*, 1998). A decrease in perimetric threshold of the fovea was found to exhibit a statistically significant correlation with increasing spherical refractive error alone but not increasing AXL. When individual stimulus locations were analysed in isolation, only one demonstrated a statistically significant correlation. This location was ten degrees from fixation in the temporal field, close to the physiological blind spot. There was no relationship between AXL and drop-off in visual field sensitivity in any quadrant of the visual field. There are clinically observable indications that myopia related stretching does seem to occur at retinal level. These include tigroid fundi and optic disc crescents, which have increased prevalence in myopic eyes (Logan *et al.*, 2004b). Modern techniques have also made it possible to quantify structural changes at a cellular level. Histological (Grossniklaus *et al.*, 1992), psychophysical (Chui *et al.*, 2005, Chui *et al.*, 2008) and adaptive optics camera studies (Kitaguchi *et al.*, 2007) of cone density in humans have shown increased photoreceptor spacing in highly myopic eyes and eyes with increased AXL compared to those with emmetropia or mild to moderate myopia, with 15 dioptres of myopia approximately doubling the spacing between retinal neurons (Chui *et al.*, 2005; Kitaguchi *et al.*, 2007). It, therefore, does not seem unreasonable to propose that retinal stretch may be occurring in the myopic eyes in this study. Nevertheless, the change is of a magnitude undetectable by this experimental paradigm except at the fovea and one stimulus location ten degrees temporal to fixation. It should also be noted that alongside decreasing photoreceptor density, a mechanical increase in AXL may also cause physical damage to or the misalignment of photoreceptors. This would have the potential

to affect light sensitivity as photoreceptor cells are known to be direction specific (Stiles-Crawford effect) and thus will only respond to light when in a specific fixed alignment. Furthermore, spatial summation may have an influence on negating the effects of retinal stretching, but the mechanism and nature of this potential effect is currently unknown and unmeasurable in this paradigm.

An inherent limitation of all studies using perimetry is that short-term fluctuation (SF) in the visual field threshold may be greater than the change that is being attempted to be measured. SF represents the scatter observed when the same threshold is repeatedly measured during a single perimetric examination (Bebié *et al.*, 1976; Flammer *et al.*, 1984). Typically in normal subjects it is approximately 2 dB (Cubbridge *et al.*, 2002; Wild *et al.*, 1998) which may have masked changes in sensitivity due to alterations in AXL. It may be the case in this study that the change is being masked by this effect. Although sample size calculation indicated 31 participants were needed, the SF value used was taken from the literature, and as such may not be accurate for or representative of the characteristics of this sample. The fact that there is a statistically significant correlation between mean spherical error and light sensitivity but not for AXL though this is approaching significance is further indicative of a sample size effect. This discrepancy may be a result of refractive error not being entirely axial in some study participants. The majority of studies have found that the SF is dependent upon eccentricity (Brenton and Phelps, 1986; Greve and Wijnans, 1972; Heijl *et al.*, 1987; Werner and Drance, 1977). This has the potential to contribute to the lack of correlation in the more eccentric stimulus locations. Another reason for this may be because there is more sensitivity to small increments of change at the fovea as a result of receptor fields being larger in the periphery.

Optical considerations should also be taken into account, and it should not be assumed that retinal stretch is the only factor with the potential to reduce visual performance in myopia. The increased AXL in myopic eyes may induce inaccuracy in perimetry by affecting luminance levels at the retina. It is also known that traditional optical correction for central myopia precipitates peripheral retinal defocus, owing to the non-spherical shape of the eye (Mutti *et al.*, 2000). Myopic eyes exhibit relative hyperopic peripheral defocus, whereas hyperopes generally experience relative myopic peripheral defocus. This also has potential to affect sensitivity to light by the same mechanism by which central defocus reduces visual sensitivity. Optical aberrations can limit visual acuity in emmetropes (Campbell *et al.*, 1965). Myopic eyes have increased monochromatic aberrations (Applegate, 1991), which could limit visual resolution on top of the limits imposed by increased neural spacing. The issue of visual field sensitivity in ametropia may be further complicated by the consequences of optical magnification. Corrected axially myopic eyes experience a reduction in retinal image size. Consequently, there is an increase in the retinal spatial frequency of stimuli thus potentially leading to inaccurate recordings by lowering neural contrast sensitivity and reducing visual performance (Chui *et al.*, 2005). However, this effect is not expected to significantly impact on the results of this study as only one participant wore spectacle correction, while the other non-emmetropic participants wore contact lens correction which is known to avoid these magnification effects.

In summary, the results of this study indicate that at the fovea, light sensitivity decreases as the degree of myopia increases, perhaps due to an increase in photoreceptor spacing, giving support to the global expansion, posterior pole expansion and axial expansion models of myopia induced retinal stretch. This effect was also seen at ten degrees temporal to fixation in the visual field. This area is known to be close to the physiological blind spot, and therefore this result may be reflective of structural differences in this

region. However, a significant correlation between myopia and visual field sensitivity could not be detected by this study design at more peripheral stimulus locations in the visual field, perhaps because of increased threshold variability in the periphery and the influence of short-term fluctuation.

8. DISCUSSION

Myopia is the most common ocular condition worldwide, and rather than being merely a refractive anomaly, is a recognised major cause of visual impairment and blindness (Resnikoff *et al.*, 2008). No 'safe' level of myopia has been identified (Flitcroft, 2012), and it carries an increased risk of associated pathology such as chorioretinal abnormalities, cataract, and glaucoma at all levels (Saw *et al.*, 2005). This, coupled with the sharp increase in myopia prevalence documented in recent years means that better understanding the epidemiology and structural and functional differences in these eyes is imperative.

Most cases of myopia which onset in childhood are due to an increase in AXL as a consequence of vitreous chamber elongation (Mutti *et al.*, 2005). The causation and inheritance pattern of myopia is unclear and is clearly multifactorial, known to be influenced by genetics, behaviour and the environment (Mutti *et al.*, 1996; Radhakrishnan, 2008; Schaeffel *et al.*, 2003). Both optical and non-optical interventions have been trialled which aim to limit myopia progression in childhood. By better understanding the mechanism which drives myopia it may be possible to optimise myopia control modalities or even prevent myopia from developing in the first instance.

This thesis describes the rationale, study design and results of a collection of cross-sectional studies which aimed to investigate the influence and associations of various structural and functional parameters on the development of myopia in children. These differences were investigated to aid a deeper understanding as to the aetiology of ametropia and subsequently underpin current research attempting to achieve the amelioration of myopia.

The correlation between refractive error and AXL is well established in both adult and child populations. However, ethnicity has been found to have a significant impact on the correlation in Australian children (Ip *et al.*, 2007). The study presented in Chapter 4 of this thesis aimed to determine the correlation in a UK population of varying ages. Determining the interplay between AXL and refractive error is an important consideration in studies investigating the effects of myopia control, particularly when considering target treatment age and efficacy. Refractive error and AXL data were collected from six to seven year old children, 12 – 13 year old children and adults aged 18 - 25, and the correlations were compared. Refractive and axial component dimensions were found to be consistent with previous studies. The correlation coefficient between AXL and MSE became stronger as the age of the cohort increased, with 1mm of axial expansion having a more profound effect on refractive error in children than in an adult population. This finding is coincident with an elongation of mean AXL as the cohorts increase in age, and is likely a reflection of the predicted reduction in Rx: AXL ratio forecast by the optical theory. It is clear that estimations made for the change in eye size per dioptre increase in myopia should be related to the distribution and magnitude of myopia in a population. The use of an arbitrary value should be applied with caution in a clinical setting and not be used to approximate the efficacy of myopia control interventions in myopia research, as the use of an inappropriate ratio has the potential to either obscure or overestimate the effect of the treatment modality. This study found that gender and ethnicity had no influence on the AXL: RX ratio, suggesting that despite known differences in the prevalence of myopia that are known to occur alongside these demographic characteristics the mechanism by which the myopia is developing in these cases is the same.

The prevalence of corneal and refractive astigmatism between these three differently aged cohorts was also investigated. No difference was found in either the prevalence or

magnitude of refractive astigmatism between age groups, which supports the findings of previous work that refractive astigmatism appears to remain relatively stable between the ages of five and 15 years (Harvey *et al.*, 2006; Hirsch *et al.*, 1963; Huynh *et al.*, 2007; Kleinstein *et al.*, 2003; O'Donoghue *et al.*, 2011). The prevalence of refractive astigmatism over 1.00 DC was found to be approximately midway between those reported by the SMS (Huynh *et al.*, 2007) and NICER (O'Donoghue *et al.*, 2001) studies. This study suggests that in childhood the degree of refractive astigmatism is linked more with hyperopia than myopia, with children with hyperopias greater than +1.91 DC demonstrating significantly higher levels of refractive astigmatism. This corroborates previous studies which have reported that hyperopic eyes are more likely to be astigmatic than myopic eyes (Baldwin and Mills, 1981; Dobson *et al.*, 2007; Garber, 1985). It also appears that the degree of refractive astigmatism in children and adults does not appear to be influenced by variations of ethnicity, gender or axial length. When the orientation of the axes of astigmatism were categorised as either 'with the rule', 'against the rule' or 'oblique', it was found that higher levels of both corneal and refractive astigmatism were more likely to be 'with the rule' for children and 'against the rule' in adults. This finding may be protective against the development of astigmatic amblyopia. Ethnicity and axial length had no significant influence on axis categorisation.

Although current trials are attempting myopia amelioration by manipulating the peripheral image through modalities such as contact lenses, (Sankaridurg *et al.*, 2011) a deeper understanding of the level of mediation the peripheral retina holds on the emmetropisation mechanism in humans is critical to underpin this work. To ascertain the relative contributions of the central and peripheral retina in the developing eye, eye structure and function in children with normally developing eyes and children with certain retinal pathologies was compared. Due to a very small sample size, comment is limited,

but AXL data from the four participants with peripheral retinal dystrophy appeared grossly normal with regards to their position relative to the normative data and the line of best fit. Myopia in these individuals seems axial in nature. Peripheral refraction findings were largely typical of peripheral refraction patterns from previous studies of children and young adults without ocular disease. The restriction of the visual field in the participants was not wildly dissimilar from the iatrogenic peripheral visual field deprivations induced in Smith *et al.*'s 2005 study which deprived the periphery of primate eyes of form vision. Visual field statuses in RP and CSNB appear to be within a range to provide useful models for comparison with animal work in this respect. Overall, this study suggests the RP and CSNB in children appear appropriate models for the investigation of the influence of the retinal periphery on emmetropisation in humans. Though recruitment was limited and a future large scale longitudinal study is recommended, this study has shown that this nature of data collection in child participants with RP and CSNB is feasible.

Magnetic resonance imaging has shown that the human eye is spherical in shape prior to the posterior 25% where there are characteristic changes in conformation (Singh *et al.*, 2006). The effect that AXL variations in ametropia have on retinal function in terms of differential light sensitivity was investigated in adult eyes, with the aim of gaining further insight into the mechanisms and nature of myopic axial growth. A statistically significant correlation was found between foveal AXL and refractive error, which is concordant with previous work (Bullimore *et al.*, 1992; Chui *et al.*, 2008; Grosvenor and Scott, 1993; Strang *et al.*, 1998). A decrease in perimetric threshold of the fovea was found to exhibit a statistically significant correlation with increasing spherical refractive error alone but not increasing AXL. When individual stimulus locations were analysed in isolation, only ten degrees from fixation in the temporal field, close to the physiological blind spot had a statistically significant correlation. This suggests that retinal stretch may be occurring in the myopic eyes in this study. Nevertheless, the change is of a magnitude

undetectable by this experimental paradigm except at the fovea and ten degrees nasal from the fovea. The results of this study indicate that at the fovea, light sensitivity decreases as the degree of myopia increases, perhaps due to an increase in photoreceptor spacing, giving support to the global expansion, posterior pole expansion and axial expansion models of myopia induced retinal stretch. This effect was also seen at ten degrees temporal to fixation in the visual field.

8.1 Future work

All of the studies presented in this thesis would have benefitted from a larger sample size. Several factors contributed to the difficulties recruiting participants. Firstly, due to staffing limitations and a busy out-patient department, recruitment of participants through the HES was difficult. Ethical restrictions also meant that screening was problematic, particularly owing to the narrow and complex inclusion criteria. There exists no centralised database for researchers to locate potential participants, so screening was limited to patients booked into clinic appointments, which means many children with retinal pathology on long recall intervals are likely to have been missed. Many of the children who attend the HES have multiple, regular appointments, so parents may be hesitant to participate in further research. The use of cycloplegia may also have factored in the low recruitment rate.

Extending the works presented in Chapters 4 and 5 of this thesis to be longitudinal would allow for the development of appropriate charts matched for a population's refractive characteristics, derived from normative ocular component data. Such charts could include an adult AXL or refraction predictor similar to those currently available for predicting adult height and stature. This may be of use when explaining and answering a parent's concerns and worries about myopia progression and end point of refraction. Another advantage of such a tool would be that the risk of myopia progression could be

identified from a range of children with similar refractive characteristics. These tools would also be of use in a research or myopia control setting to help ascertain how effective a treatment is at retarding myopia progression opposed to normal refractive and axial length development.

This thesis also suggests that RP and CSNB in children appear appropriate models for the investigation of the influence of the retinal periphery on emmetropisation in humans. Having a large-scale longitudinal version of this study too, would elucidate further if the findings from animal studies can be applied to humans. Extending the study to be longitudinal would allow for the effect of progressing tunnel vision in RP to be assessed with regards to its impact on refractive and AXL development. A multi-site study of perimetry, axial length and refractive error in participants with RP and CSNB is suggested. ERG and OCT were not used in the current study, but would be useful tools to determine the state of retinal integrity and function in these participants. Future work should ensure close age matching with healthy-eyed controls for improved accuracy.

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10. APPENDICES

10.1 Ethical approval for study described in Chapter 7

PhD Student Ethics Application 447

The status of this Application is now "Final" It can no longer be edited by the author. The details provided in Section B suggest this project carries a relatively low risk in relation to ethical issues and is appropriate for "Self-Certification". A record of the project will be stored on the University Ethics database and you should note that the School Ethics Committee and/or the University Ethics Committee may contact you in future when undertaking audits and reviews of the Ethics approval procedures. You may be contacted by the Ethics Committee if any aspects of your application require clarification.

Submitted by ~~cruicksf~~ on Mon, 2012-11-12 10:31

Section A

A1	Title Of Research (max 20 words):	The influence of axial length on normal visual field function.
A2	Proposed Study Dates: Start Date	1 February 2013
A3	Proposed Study Dates: Finish Date	1 December 2014
A4	Project Supervisor details:	
A4a	Project Supervisor details: Title and Name	Dr Nicola Logan
A4b	Project Supervisor details: Email Address	n.s.logan@aston.ac.uk
A4c	Project Supervisor details: Telephone	0121 204 4128
A5	School	
A6	Student details:	
A6a	Student details: Name	Fiona Cruickshank
A6b	Student details: Email Address	cruicksf@aston.ac.uk

10.2 Participant information sheet – (Chapter 7)





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10.3 Participant consent form – Chapter 7



10.4 Confirmation of sponsorship from Aston University research ethics committee for project ocular development in children (Chapter 6)



10.5 Confirmation of favourable ethical opinion from NRES committee West Midlands for project ocular development in children (Chapter 6)





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**10.6 Confirmation of ethical approval from Birmingham Children's Hospital
research and development (Chapter 6)**



10.7 Confirmation of approval of minor amendment for project ocular development in children (Chapter 6)





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10.8 Study protocol for project ocular development in children (Chapter 6)





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**10.9 Child information booklet for project ocular development in children
(Chapter 6)**





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10.10 Parent/Guardian information sheet for project ocular development in children (Chapter 6)



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10.11 Adult participant information sheet for project ocular development in children (Chapter 6)





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10.12 Child consent form for project ocular development in children (Chapter 6)



10.13 Child assent form for project ocular development in children (Chapter 6)



10.14 Parent/Guardian consent form for project ocular development in children (Chapter 6)



10.15 Parent/Guardian consent form for project ocular development in children (Chapter 6)

